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Old and New Pathways in Human Genetics[1]

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THE year 1950 rounds out the first half-century of the modern science of genetics. During these fifty years this branch of biological science has grown and developed until it, too, has its own branches and subdivisions. Meanwhile, lines of demarcation originally existing between genetics and other sciences have gradually disintegrated until now genetics merges imperceptibly into many other fields. Agricultural genetics, physiological genetics, developmental genetics, biochemical genetics, radiation genetics, cytogenetics, population genetics, and human and medical genetics have all emerged as coordinated fields of research, and each has made notable contributions to knowledge and to human welfare.

Although speculations on matters of heredity may be found far back in human history, and although the pioneer researches of Mendel are now nearly one hundred years old, modern genetics dates only from the turn of the century. When Mendel's principles had been rediscovered and had been tested on various experimental organisms, when the cytological basis for the phenomena had been recognized, and when the earlier basic principles had been expanded, extended, and woven into an understandable pattern, it was inevitable that an attempt should have been made to determine the applicability of these principles to man.

During the first decade of the century the literature on human genetics began to appear under such names as Ballowitz, Bulloch, Davenport, Drinkwater, Farabee, Fischer, Folkar, Galton, Garrod, Gossage, Guthrie, Guyer, Harmon, Holmes, Hurst, Nettleship, Pearson, Vogt, Weinberg and Wilson. During this decade there was begun the publication of the valuable *Treasury of Human Inheritance* under the editorship of Karl Pearson. While some of the studies had a strong eugenics slant, others dealt with human genetics *per se*.

It quickly became apparent that Mendel's principles were indeed applicable to man, and the discovery of new and more complicated principles through the years has served only to strengthen and further document the conclusion that the genetics of man is essentially like that of other organisms. Virtually

[1] Presidential address to the American Society of Human Genetics, delivered as part of the Golden Jubilee Celebration of Genetics at Ohio State University, Columbus, Ohio, on September 12, 1950.

every basic law and principle of modern genetics can be illustrated with human material, and some of these principles have in fact been derived from data on man.

In spite of the flurry of interest in human heredity during the first decade or two of the century, this interest, particularly in America, was short lived. The rise of the experimental method in genetics with its prospect of definitive results within reasonable time limits caused many geneticists starting out on their careers to feel a hesitancy towards forsaking experimental work, and to fear that they might be embarking on non-scientific procedures in taking up the study of human heredity. As a result, the programs of the Genetics Society of America for the ten years following its inception carried a scant dozen papers on the genetics of man.

On the last day of the year 1941 there was held at the Dallas meetings of the A.A.A.S. a symposium on human genetics, jointly sponsored by the American Society of Naturalists, the Genetics Society of America, the American Society of Zoologists, and the Botanical Society of America. Following this symposium, interest in the study of human heredity in America gradually increased. The old Eugenics Record Office at Cold Spring Harbor, which had faded from the picture in the face of a growing skepticism regarding the eugenics movement on the part of many geneticists, was replaced in this country by such centers of research in human genetics as the Ohio State University, the University of Michigan, the Bowman Gray School of Medicine, the University of Minnesota, the University of Chicago, the New York City Examiner's Office, and the New York State Psychiatric Institute. Other centers are developing rapidly. The culmination of these activities in America was the formation of the American Society of Human Genetics in 1948, an event which holds promise of a true flowering of the subject on this side of the Atlantic.

Meanwhile various European laboratories had been far-sighted enough to perceive the importance of the study of human heredity, and centers of activity there had grown apace. Those in Germany and Russia were unfortunately detoured or terminated due to considerations of war or of conflicting ideologies, but those in England, Sweden and Denmark, and to some extent in Switzerland, Holland and other parts of Europe, are continuing to function at a high degree of efficiency. The recent formation by the International Union of Biological Sciences of a subsection on Human Genetics offers great hope that there may soon be a complete revival of international cooperation in the study of human heredity.

Within the last few decades remarkable progress has been made in the analysis of the genetics of man. The earlier studies dealt almost exclusively with individual families, and were concerned largely with conspicuous phenotypic discontinuities. If the trait were sufficiently striking and readily identified

data were often obtainable for several generations back. The families were of necessity selected, only those families containing at least one affected member being included in the studies. This, of course, created a bias in the data, but in spite of it many anomalies and diatheses were shown to have genetic bases, and for some of them presumptive evidence was obtained for specific types of hereditary behavior.

The discovery of the human blood groups by Landsteiner and the remarkable extensions of the original discovery by Levine, Wiener, Hirszfeld, Bernstein, Race and others opened the way to an entirely new approach to human genetics: the population approach. The blood groups have been to human genetics what Drosophila has been to classical genetics. The first of the many important contributions which the study of blood groups made to the field of human heredity was the providing of "test characters" for analysis. Test characters are normal traits which can easily and accurately be ascertained, which are dependent upon a single pair or set of alleles, which are relatively uninfluenced by nongenetic impacts, and in which both or all alleles of the set are present in the population with reasonable frequencies.

In the study of test characters, the data are collected wholly at random, that is, without regard to the phenotypes of the individuals. The data may represent only individuals in the population, without regard to genetic relationship, or they may be in the form of families or kinships. Both kinds of data are valuable, each in its own way. When families are investigated in this manner, it is with the assurance that the majority of them will exhibit intrafamilial variation. The many blood agglutinogens are of this nature, as is the taste deficiency to phenyl-thio-carbamide (12, 65).

Test characters present the student of human heredity with problems not encountered by the laboratory geneticist. In the laboratory or field plot, where selection and inbreeding may be freely practiced, relatively isogenic, true-breeding lines may be established. From such lines we may, by controlled matings, obtain classical genetic ratios, and thus determine the mode of inheritance involved in any specific trait, and the genotypes of particular individuals, with relative ease.

In man, however, we must work with highly heterozygous material which is frequently restricted to two generations, and sometimes to but one, and in which the genotypes are in many cases capable only of incomplete specification. Under these circumstances even well-classified data will often contain mixtures of genotypically different types of matings.

The approach to the solution of such problems constitutes one of the most important milestones in the history of human genetics. In 1925 Bernstein, by means of cleverly designed extensions of the Hardy-Weinberg law of equilibrium, showed that data on test characters are subject to rigorous mathematical analysis on the basis of the frequencies of the postulated genes in the

population. The immediate outcome of Bernstein's studies was his proof that the ABO blood groups are inherited on the basis of a set of triple alleles, and not, as had previously been thought, on the basis of two pairs of genes. The long range outcome of these studies, however, has been the development of population genetics as an important area of research.

Gene frequency analyses for many types of transmission in populations were rapidly developed by Cotterman, Haldane, Lenz, Hogben, Snyder, Wellisch, Wiener and others. To such an extent have these methods developed that, as Cotterman has pointed out, unit factor inheritance may be detected in data comprising but a single generation, that is, in sibships of completely unspecified parentage. Thus in the course of the development of methods for analyzing the genetics of man, the required number of generations has been reduced first to two, and finally to but one, while the requisite knowledge of parental genotypes has been gradually reduced and finally eliminated altogether.

It must not be thought that methods which lessen the required number of generations or which minimize knowledge of parental genotypes are as desirable or efficient as classical methods. Such methods merely serve, as efficiently as possible, in an area in which test matings with precisely known genotypes are not available.

It is obvious that the methods of population genetics are not applicable to single families, and will not automatically correct the bias resulting from the selection of families on the basis of the inclusion of at least one affected member. Haldane, Hogben and others, however, have provided correction factors for cases of this sort, and such instances may now be analyzed efficiently.

Meanwhile a determined effort was being made to study linkage in man, and to map the human chromosomes. Here further new problems presented themselves. It was soon apparent that in dealing with human material, just as a single phenotype will often include two indistinguishable genotypes, so a single heterozygous genotype will include two indistinguishable phases, coupling and repulsion. This seemingly insurmountable difficulty was solved with increasing degrees of efficiency by Bernstein, Wiener, Haldane, Fisher, Penrose, and finally by Finney. The mathematical methods used are monuments to the ingenuity and ability of biometricians, and have helped to repay the debt which human genetics owes to other sciences. By the use of such methods a start has been made on the mapping of human chromosomes (71).

The original methods devised for studying the dynamics of gene frequencies were based on the assumption of infinitely large populations in equilibrium. But man is a gregarious animal, and tends to cluster in groups of limited size. Within restricted populations sampling fluctuations, which constitute a characteristic of the genetic mechanism as inherent as any of its other properties, may have rather surprising effects.

Natural populations which at first sight may appear to be very extensive

are in fact often composed of numerous local and more-or-less self-contained breeding units (isolates). In a completely self-contained unit, the gene frequency dynamics will be determined by the size and mating pattern of the unit. Where some intermigration occurs, the evolution of the over-all population will depend in important ways on the numbers in the individual subgroups and on the extent of the intermigration. Among the hundreds of millions of human beings whose distribution is practically continuous over the earth's surface there are countless isolated rural groups which contribute only occasional migrants to other populations. Even in urban areas isolates occur on the basis of social class, religious affiliations, culture patterns and other isolating mechanisms. The mating patterns of mankind are in fact those imposed by the occurrence of many partial isolates. Dahlberg has roughly estimated from the frequencies of various types of consanguineous marriages that the average effective mating number of such quasi-isolates in Europe lies somewhere between 400 and 3000, and this figure may be taken as applicable to America also. In earlier centuries the numbers must have been even smaller.

Considerations such as these lead to important conclusions regarding human genetics. While sampling fluctuations would be likely to result only in negligible shifts in gene frequencies from generation to generation in large populations, they may in small populations of a few hundred or less bring about radical alterations in gene frequencies quite aside from mutation or selection.

It happens, moreover, that the sampling fluctuations tend to be cumulative in their effects. Since the sample of genes drawn from the supply of any generation must in turn generate the supply from which a new sample will be drawn when the progeny reproduce, the allele which is less frequent in the parental generation tends to have its frequency further reduced in progeny resulting from samples drawn from the supply. Such cumulative changes result in what is known as genetic drift. It can lead to the spread of a new mutant gene through a small population, or, more often, to the loss of a new allele before it has had a chance to spread appreciably or at all.

The human geneticist today must therefore describe variability in two categories: that of the individual and his kinship, and that of the population. The individual and the members of his family are to be described in terms of *Mendelian genetics;* that is, in terms of the presence or absence of specific alleles, plus, of course, the results of environmental circumstances. The population, on the other hand, is to be characterized in terms of *population genetics;* that is, in terms of the relative proportions of various alleles, and of the over-all environmental impacts.

Among the basic principles of population genetics which are essential to the working materials of the modern student of human heredity are the following ('69):

1. Classical Mendelian ratios are not to be expected in random samples

drawn from a population, nor even necessarily from classified data including the pooled offspring from phenotypically similar matings. Classical ratios are to be found only among the offspring of an individual family if there are sufficient children, or among the pooled offspring of a series of families where the parental mating type of each family is in fact genotypically identical with that of every other family. Since the genotypes of human beings are seldom capable of specification, even the best classified data will usually contain mixtures of genotypes and must not be expected to yield Mendelian ratios.

2. In spite of the absence of classical ratios, predictable ratios of another sort do occur under the conditions stated above. These ratios are population ratios, and are expressed in terms of the proportions of the alleles. They are dynamic ratios in contrast to static Mendelian ratios. Among random matings of individuals exhibiting a trait due to a dominant gene, for example, there will be some in which one or both parents are homozygous, resulting in the Mendelian ratio of dominants to recessives of 1:0, and others in which both parents are heterozygous, resulting in the Mendelian ratio of $\frac{3}{4}:\frac{1}{4}$. In a random-mating population these static ratios are jointly expressed as one dynamic population ratio, $[(1 + 2q)/(1 + q)^2]:[q^2/(1 + q)^2]$ where q is the proportion of the recessive allele in the population (66). Many similar population ratios have been derived and are of the utmost value in the analysis of human genetics.

3. The comparison of predicted and observed population ratios can be used to estimate the number and kind of genes responsible for a hereditary variation in a population just as the comparison of predicted and observed Mendelian ratios can be used to estimate the number and kind of genes involved in a laboratory experiment. Goodness of fit tests have been formulated for many such estimations.

4. The inherent characteristics of the Mendelian mechanism are such that in a large population in which the effects of mutation, selection, and in-and-out migration are either negligible or balancing each other, the proportions of the various genes will remain constant from generation to generation, regardless of the dominance or recessivity of each gene. If there is in addition random mating in a constant environment, the proportions of the genotypes, and thus of the traits produced by them, will likewise remain constant.

5. Changes in the proportionate occurrence of genes or traits can be brought about, however, by various phenomena including mutation, selection, inbreeding, assortative mating, migration and, particularly in isolates, genetic drift. The rates and extents of such changes are capable of mathematical estimation. The methods have been summarized in recent books by Dahlberg, Hogben, Li and others.

6. The occurrence of genetic linkage between the genes for two traits does not change the association between those traits in the population from what it

would be if they were not linked. Stated conversely, a correlation between two traits in a free-breeding population does not indicate genetic linkage between the genes responsible for the traits.

7. The inherent characteristics of the linkage mechanism are such, however, that the occurrence of linkage may be detected without recourse to the classical distinctions between coupling and repulsion phases, by means of specially constructed methods applicable to human material.

Unfortunately theoretical considerations of population genetics are far in advance of empirical investigations. There is as yet insufficient realization of the necessity of carefully collected field data on the genetics of human populations. The realization is growing, however, and is even beginning to invade the related fields of anthropology and medicine. The recent Cold Spring Harbor symposium on the origin and evolution of man brought together anthropologists, physicians, and geneticists, and has done much to point the way to cooperative field efforts.

Even with the limited population data now available, however, one clear conclusion seems to be emerging (69, 70). Human populations differ one from the other almost entirely in the varying *proportions* of the allelic genes of the various sets of hereditary factors, and not in the *kinds* of genes they contain. The extreme positions held by those who on the one hand maintain that there are no significant genetic differences between human races, and those who on the other hand hold that certain races are "superior" and others "inferior", require drastic modification in the light of the accumulated data on the gene frequency dynamics of human populations.

Throughout the growth and development of human genetics there have been other mistaken beliefs to be corrected. One of the earliest and farthest-reaching fallacies in the philosophical approach to human problems was the belief that if a genetic basis were demonstrated for a certain trait, that trait could not be subject to enviromental modification; and conversely, if a trait were shown to be influenced by the environment, it could not at the same time be genetically determined. Although many of us have for years called attention to this fallacy, it still crops up in the literature, especially that of medicine, sociology, psychology, and education.

There is usually an element of fear present in the case of the heredity-environment fallacy. For the physician, there may be a certain reluctance to accept the genetic basis for a disease or anomaly on the grounds that it would thereby be useless to attempt therapy. For the sociologist or psychologist, the reluctance involves the fear that new or changed attitudes could not be brought about if there were any genetic basis for the original development of individual differences in behavior. The fallacy appears in subtle ways and is not always easy to detect. In a recent book on Intergroup Relation Centers (9), the author states that hostilities and methods of expressing animosities are not born in children,

and therefore they can be controlled (italics mine). It may indeed be true that such things are not born in children, but even if they were, this would not determine that they could not be controlled.

The same author states that science proves that differences in knowledge, customs, and personality are not transmitted biologically. Science proves no such thing. There is little significant scientific evidence either way on the possible genetic basis for personality, but there is a patent fear, on the part of the author of the statement, that if there were such a basis, intergroup relations centers might lose their usefulness.

Two psychologists who recently maintained that massive doses of vitamin A would cure colorblindness wrongly concluded from their studies that it is "obvious that red-green colorblindness is not the simple Mendelian trait that popular theories assume it to be" (18). When the results were attacked by another psychologist (50), this worker upheld the postulate that "certain anomalies of color vision are both hereditary *and incurable*" (italics mine), thus using the same misconceived argument, but the other way around.

We must keep constantly in mind the fact that each person with all his characteristics is the cooperative result of genetic and environmental agencies. The genes and their accompanying cytoplasm do not alone make a man or woman. There is always an environment in which the individual develops, although the relative effects of differences in gene substitutions and differences in environmental forces will vary from trait to trait.

There are human genes, such as those responsible for the blood antigens, which express themselves rather uniformly within any known range of environment. There are other genes, such as those for resistance and susceptibility, the expression of which may vary considerably in different environments. It is probable that, in general, the fewer biochemical steps that intervene between a gene and its resulting trait, the less significantly will it be environmentally influenced, and the closer will be the correspondence between the presence of the gene and the presence of the trait.

It is important to make the distinction between what the gene actually does, which is apparently of a biochemical nature such as antigenic or enzymatic activity, and what the end result may be, under extragenic influences. This point of view is especially important when it is realized that the environmental events intervening between gene actions and finished characters in man may range from such overt occurrences as trauma and infection to the most subtle embryological, immunological and psychological phenomena. Furthermore, there is no reason to doubt the feasibility, and in many cases the desirability, of attempting the control of such environmental agents. The recognition of a genetic potential in many traits should serve only to broaden rather than to narrow the scope of activity of the physician, the psychologist, the sociologist, and the educator.

Moreover, the recognition of the dual action of genetic and environmental agencies in the production of finished characters makes it possible to frame the questions as to how much of the variability in a given trait in a specified population in a specified environment is due to differences in the genotypes of the individuals concerned, and how much is due to variations in the environment under discussion. The mere collection and analysis of families will offer little information on these points. Similarity or variability within families may conceivably be due as well to non-genetic agencies as to genetic factors. In addition to pedigree studies we must use methods designed to discriminate between the potential causes of the variation. Such methods involve the observation of a series of genetically diverse individuals in the same environment, and of genetically similar individuals in diverse environments.

The twin studies by such investigators as von Verschuer, Newman, Rife, and Kallmann are examples of this type of procedure. So also are the institutional and foster home studies of students such as Burks, Freeman, and Leahy. Investigations of this nature mark the beginnings of an attempt to analyze traits other than those dependent on single gene substitutions.

It was logical that the earlier studies and even the first of the new methods devised for analyzing human genetics should concern themselves with single gene effects. Such effects are often striking, easily recognizable, and are usually sharply discontinuous. They are found to occur in practically every structure, organ and tissue of the body, and in nearly all physiological processes. We now have presumptive evidence that more than 100 variations (mostly pathologic) in the skin and its derivatives, more than 100 eye abnormalities, and a comparable number of skeletal anomalies are attributable to single gene substitutions. There is reasonable evidence of single gene determination for a score of blood dyscrasias and for comparable numbers of aberrations of the muscular system, of nervous disorders, and of metabolic and endocrine disturbances.

On the other hand, there are remarkably few non-pathological variations in man which have been demonstrated to be the results of single gene substitutions. The blood group antigens, the taste ability and deficiency for phenyl-thiocarbamide, the direction of the fine hair of the forehead and one or two others represent a major portion of normal human characters affected by known single genes. Recent studies by Spuhler, Reed, Rife, and others offer some hope that this list may be augmented.

At any rate our precise knowledge of human genetics is largely confined to the effects of single gene substitutions. Among other known facts about such characters is the discovery that they can be simulated by the effects of appropriate environmental agencies in the absence of the gene. The resulting "phenocopies" are often indistinguishable from the effects of the genes themselves In human material, certain conditions apparently occur as single-gene effects in some families and as phenocopies in others; for example, the skeletal and

neurological anomalies following irradiation (49), the eye defects as sequellae to infection such as rubella (28), and the simulated heart troubles brought on by environmentally conditioned anxiety reactions (70).

Finally it has been shown that the effect of a gene substitution at any locus may be influenced by the genes at many other loci, and that conversely most single genes have multiple effects, often on viability, in addition to some major action.

It is tempting, in the face of the striking and variable effects of single-gene substitutions, to suppose that collectively they play a major role in human genetics. It is becoming more and more apparent, however, that single-gene differences resulting in marked phenotypic discontinuities are not in fact the most common type of genetic variability. Among the effects of radiation on gene mutation, for example, are some conspicuous phenotypic effects apparently identical with spontaneous mutations; a larger number of lethal mutations; and the largest number, by far, of mutations, the only discernible effects of which are slight changes in viability, vigor, or other physiological activities. Natural mutations appear to be distributed over a similar spectrum.

Probably both morphological and physiological characters affect viability, and there seems to be a general parallelism between the conspicuousness of the visible effect of a gene and the degree of viability impairment which results. Broadly speaking, the more striking the effect, the greater is the reduction in viability. Thus the largest class of mutant genes is composed of those genes which individually do not have readily discernible phenotypic effects, but for which the cumulative effects may be quite demonstrable.

Although most of the characteristics in man which have been adequately analyzed from the genetic standpoint are pathological discontinuities, the significant differences between individuals and between populations are to be found in such things as intelligence, special abilities, social behavior, size and features. These are traits of a non-pathological nature; moreover, they follow a continuous distribution rather than a discontinuous one. Insofar as they have a genetic basis, therefore, they must depend upon multifactorial heredity involving cumulative effects of genes.

The importance of the problems of dealing with such cumulatively acting genes has so impressed Mather and his colleagues that they have designated genes of this sort *polygenes*. It is assumed that the effect of an individual gene of a polygenic series approaches the limit at which it can not be distinquished from an environmental increment. In contrast, the single genes responsible for conspicuous phenotypic discontinuities are called *major genes*. It is possible to identify the latter individually, and to assign them to precise loci and specific linkage groups.

Polygenes, on the other hand, can not be individually so identified and so localized. Their effects appear to be quantitatively equivalent and cumulative.

Their existence must be accepted, however, if for no other reason than the effectiveness of selective breeding for almost any continuously variable quantitative character in a genetically heterogeneous population. There is, moreover, evidence that polygenes, like classical major genes, undergo segregation and crossing over.

If then, as seems clear, genes with individually minute but cumulatively appreciable effects constitute the largest class of available mutant genes, much of the genetic variability of man is contingent upon multifactorial inheritance. Not only most of the genetic variability, but most of the resulting phenotypic variability as well, must depend upon such genes, since natural selection tends to keep at low incidences the large discontinuities produced by major genes, because of the viability impairment connected with them.

Almost the only discernible single-gene differences which are found at appreciably high frequencies in human populations are those which appear to be approximately neutral in their viability effects. The genes concerned are those for the blood group antigens, taste deficiency, color vision, hair whorl, and similar neutral factors. The genes for thalassemia and for sickle cell anemia which have recently been so carefully studied by Neel, present exceptions for which we do not at present have a clear explanation. In these instances a relatively high frequency of the traits has been maintained in the face of the elimination or decreased fertility of the affected homozygotes. Whether an inordinately high mutation rate, a selective advantage of the heterozygote, or some other explanation, will be found to apply, only time will tell. Recent evidence from Reed's laboratory (61) that fibrosis of the pancreas presents a similar situation raises the possibility that mutation rates in man may prove to be higher than has been realized. Nevertheless, of the hundreds of severe abnormalities in man which may be attributable to single-gene substitutions, only a few have population incidences above one in ten thousand, and the vast majority have very much lower occurrences than this.

In a recent discussion of these problems, David and I (15) suggested that if two unrelated people were picked at random from a population, or even one from each of two populations, they might be found to differ in respect to one or another of the blood antigens, and one might be a taster of phenyl-thio-carbamide and the other a non-taster. Beyond this it is highly probable that few if any of the observable phenotypic differences between them would be referable to known major genes. And yet we know at least the physical differences to be largely genetic because of the almost complete physical identity of the members of any pair of monozygotic twins.

It follows that the major part of such genetic differences as are involved in the non-pathological range of human variability is most probably multifactorial in nature. Recognition of this fact may set limits to the amount of information

which we may expect to gain through continued analysis of single-gene differences.

I would be the last one to suggest that we should cease searching for and describing individual gene effects. It is essential that we continue to develop and refine the methods for detecting and analyzing the activities of major genes in human populations. Such analyses provide, among other things, as I shall shortly describe, valuable practical applications in medicine.

But, as David and I have recently pointed out, if human genetics is to progress along fresh pathways, the traditional atomistic approach must be supplemented by new methods which will provide information on multifactorial inheritance. We must be able to analyze genetic variability without recourse to classical single-gene analyses. The newer types of twin and twin-family studies appear to be a fruitful approach for this kind of investigation. Although the technics need elaboration and refinement, much progress is being made through quantitative comparisons of intra-pair differences in monozygotic and dizygotic twins separated and together, twin-family analyses, and the use of co-twin controls.

If the anthropologist, the psychologist, the sociologist, and the geneticist are to join forces in the genetic analysis of racial traits which are significant on the level of intelligence, personality, and social behavior, the implications of multifactorial inheritance must be carefully studied. Such transmission would seem, for example, less likely to bring about phenotypic differentiation through genetic drift than would the transmission of major genes, since the effects of individual multifactorial genes are apparently in large part mutually interchangeable. Even though genetic drift should result in the accumulation of different constellations of such genes in various populations, the overall phenotypic manifestations would tend to remain constant, since the relative proportions of plus and minus genes should be about the same from one population to the next. Even in occasional instances where genetic drift does lead to phenotypic differentiation between small populations, this would have little chance of persisting after the populations expanded, unless it had a high adaptive value. As Dolzhansky and Montagu have pointed out, flexibility and plasticity of behavioral adjustments are likely to have had selective advantages over fixed or stereotyped responses in human intelligence and social behavior.

I can not close this discussion without some reference to the important advantages to the health and welfare of mankind which have accrued from our increasing knowledge of human genetics. In past years those persons who have been concerned with the progress of medicine have given their chief attention to the problems of the alleviation and control of unfavorable and deleterious agencies of the environment. Throughout the decades increasing degrees of mastery have been achieved over the harmful and debilitating effects of infectious agents, malnutrition, trauma, emotional stress, and occupational hazards.

These achievements properly stand as significant monuments to the abilities, energies, and enthusiasms of those who have accomplished so much for medicine and human welfare.

The decisive roles played by the bacteriologist in facilitating the control of infectious disease, by the biochemist in outlining the regulation of nutritional disorders, by the psychologist and psychiatrist in aiding in overcoming the harmful effects of emotional stresses, by the physician in combating the ravages of physiological aberrancies, and by the surgeon in repairing damage due to trauma and irritation, are now being paralleled by the medical geneticist, who is making possible the understanding and control of genetic disease.

The pioneering studies of such investigators as Macklin, Lenz, Roberts, and Allan have led to a wide-spread attack on the problems of medical genetics, and have resulted in a series of practical applications. Those applications include the clinical detection of genetic carriers of disease (51), the earlier and more accurate identification of morbific genetic entities (46), the instituting of therapeutic and preventive measures based on such detection and identification (68), the developing of genetic prognoses (67), and the solution of immunological problems such as hemolytic disease of the newborn (43), and of medicolegal problems such as the determination of disputed paternity (77).

Rapid progress is being made along all these lines, and it would be impossible to present details here concerning any of them. The increase in sound genetic information in the newer medical text books and the growing number of courses in medical genetics in medical schools, however, testify to the appreciation of the genetic viewpoint by the physician.

To the medical members of the society I would bring a reminder that, as Macklin has so clearly stated, when it is realized that the very early signs of a disease, so often at present unrecognized, are to be found more frequently in the relatives of a patient with an overt condition than anywhere else, these early signs will be actively searched for. Slight but significant deviations from normality, which have in the past been ignored by physician and patient alike, will take on new and important meanings in the light of genetics, giving rise to new criteria for diagnosis, earlier identification, and consequent new opportunities for prevention and therapy.

Furthermore, the detection of genetic carriers will make possible a sharpened approach to the physiology and biochemistry of disease, by providing for study a relatively large number of people in the very early stages of the conditions.

The physician is in a strategic position to obtain critical genetic data for prognoses. It is especially important that physicians should record *consecutive* series of family histories on various anomalies as the patients appear in the office, regardless of whether there is a patent familial occurrence in every case. Too often only those families are recorded and reported in which several members exhibit the disease, while the sporadic cases are not considered worthy of

publication. Yet these are the very data which make accurate genetic prognosis possible.

To both the medical and anthropological members of the society I would point out that empirical data have not nearly caught up with theoretical considerations of human genetics. We need accurate data on the frequencies of all sorts of characteristics in populations, on their distributions within families, on the physiological and biochemical activities of the genes responsible for them, on the formation of isolates within larger populations, and on the extent of inbreeding and assortative mating within such isolates and of intermigration between them. The recent reports of Böök, Boyd, Kemp, Mourant, and Penrose are excellent examples of what can be done along these lines.

The human genetic studies of the future must be cooperative efforts. Only by teamwork involving scientists from many areas can the understanding of the genetics of man be expected to advance appreciably. To those of you in related fields who are willing to lend your aid and advice to such teams, it may be confidently promised that in direct proportion to the data and information thus provided there will emerge a deeper and more significant understanding of human biology, and recurrent new practical ways in which to use the information for the improvement of the health and welfare of all mankind.

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A Twin-Family Study of Susceptibility to Poliomyelitis

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THE question of genetically controlled constitutional susceptibility to acute poliomyelitis has been discussed by several authors, notably by Aycock (1942). Although it has been proved beyond question that acute poliomyelitis occurs only with invasion of the host by the specific virus, it is equally clear that only a small proportion of the individuals exposed to the virus develop clinical signs of the disease. Aycock has reviewed a fairly large volume of data relating to the familial aggregation of cases, evaluating this in relation to the known facts concerning the epidemiology of the disease and comparing it to similar information concerning measles, scarlet fever, diphtheria and diabetes. He states that all observations are consistent with the theory that hereditary susceptibility may determine the occurrence of paralysis in a selected few of the many exposed to the virus. Several pedigrees demonstrating heavy familial aggregation of paralytic poliomyelitis, not only within a given sibship, but in related sibships widely separated geographically and in different generations, have been published by Aycock (1934, 1942). Similar pedigrees have also been published in Europe, one of the most recent accounts being that of Czickeli (1948), who cites previous similar studies. The point could be raised that such pedigrees were especially selected because they present large familial aggregations of cases, and perhaps could be expected to occur by chance alone. Although a rigorous estimate of the probability of occurrence of such extreme instances by chance alone cannot readily be obtained, it would seem rather unlikely that chance could be responsible for so many well substantiated pedigrees showing cases in different sibships so separated in time and space that contagion between sibships becomes impossible. Aycock recognizes that such pedigrees cannot be considered proof of the operation of hereditary factors, but they do present evidence which should be taken into consideration.

A somewhat different approach to the problem was used by Addair and Snyder (1942). They collected all cases of paralytic poliomyelitis with residual paralysis that occurred in an isolated section of McDowell County, West Virginia, over a period of 50 years. All 29 cases so found were shown to be related to each other, and are all listed in one large pedigree. This pedigree

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is interpreted as suggesting the existence of an autosomal recessive gene for susceptibility to paralytic poliomyelitis with about 70 percent penetrance.

In such a situation it would be expected that twin studies might provide additional evidence, probably of a more critical kind. The largest twin study found in the literature is that of Borgström (1939). Among 1592 cases of poliomyelitis occurring in Finland from 1930 to 1936, he located 17 pairs of twins, of whom at least one member of each pair had poliomyelitis while the other twin was living. Four of the twin pairs were diagnosed as monozygous and 13 as dizygous. There was concordance regarding paralysis in only 1 pair, monozygous. In six pairs (5 dizygous, 1 monozygous) there was a simultaneous illness in the second twin which might be considered "abortive" or non-paralytic poliomyelitis. In ten of the pairs (8 dizygous, 2 monozygous) the second twin had no symptoms. Borgström also summarized the case reports of twins with poliomyelitis found in the literature, citing 14 authors who collectively reported 14 monozygous pairs of whom 5 were concordant, two discordant dizygous pairs, and 6 pairs in which zygosity could not be definitely determined, of whom 4 were concordant and 2 discordant.

Aycock's (1942) data include 7 pairs of twins where zygosity is diagnosed; of 2 monozygous pairs, one is concordant regarding paralysis, and of 5 dizygous pairs, one pair is concordant and 4 discordant. Again, the available information regarding twin studies is insufficient to permit definite conclusions to be drawn with confidence.

MATERIALS AND METHODS

In the hope that a numerically more extensive study of twin pairs might give further evidence concerning the possible existence of genetically determined factors of susceptibility to paralysis in poliomyelitis, efforts were made to collect an unselected series of suitable families for study. A major problem was that of avoiding bias in selection of the pairs. Previous experience with hospital and physicians' records has convinced us that the fact that a given patient is a twin is much more likely to be recorded if both twins are ill than if only one is known to be ill. Therefore such records were not consulted in obtaining the original study group, but were sought out only after a family had entered the record from another source.

Our primary source of records was the infectious disease report card required by law to be filed with the Division of Epidemiology of the North Carolina State Board of Health by the attending physician in each case where poliomyelitis is diagnosed. Through the kind co-operation of the officials of the State Board of Health, it was possible to obtain photostatic copies of all such report cards filed during the years 1940 through 1948, totaling 4,213 cards. An attempt was then made to definitely classify as many as possible of these individuals as having been single-born or twins. Inquiry was first made

of the family physician, if still practicing in the community, regarding all cases that apparently were originally reported by him. Lists were prepared giving the name, address, age, sex, and date of illness for all patients reported by a given physician, and this list, together with a letter requesting the desired information, was mailed to the physician. The physician was requested to classify the patients on the list as twins, non-twins or unknown, and was especially requested to list individuals as unknown unless reliable personal knowledge of the family was available. Such lists were classified and returned by 786 North Carolina physicians. Additional sources of information were utilized where applicable, and inquiry was made of public health nurses, welfare workers, clinic personnel and others who might have first hand knowledge of the cases in question. Birth certificates were consulted in the records of the State Board of Health for a small proportion of the cases. Data gathered from all sources gave definite information concerning single or multiple birth for 3890 of the original 4213 cases.

By this method, 59 cases were reported to us as being members of a set of twins or triplets. Further personal investigation was then made of the 59 families so reported. Our criteria for including a family in the final group of studied cases required that (1) one or more members of the twin set should have had proved paralytic poliomyelitis, and (2) both twins should be living in the same household at the time of onset of acute symptoms, and therefore both presumably equally exposed to infection. Of the original 59 cases reported as twins, 46 families met the above criteria, while 13 families were excluded from further consideration after adequate investigation. The bases for exclusion of the 13 rejected families were as follows:

1. Twin partner deceased prior to onset of poliomyelitis in surviving twin	5 cases
2. Family moved out of North Carolina before time of survey	2 cases
3. Double report on same individual under different names	1 case
4. Incorrect report, patient with paralytic poliomyelitis had twin sibs who were not affected or had only abortive form of disease	2 cases
5. Diagnosis not acceptable:	
Non-paralytic poliomyelitis	2 cases
Other diagnosis established	1 case
Total rejected	13 cases

As will be seen from the above table, 3 of the 59 reported cases (items 3 and 4) were excluded because they were not twins. Of the 56 confirmed multiple birth cases, 55 were members of a twin pair and one was a member of a triplet set. Thus there is an observed incidence of multiple births among the 3890 classified cases of 1 in 69.46 or 1.440 ± 0.191 per cent.

The 46 families remaining who met the criteria for inclusion in this study were visited in their homes. The geographic distribution of cases is indicated on the map (fig. 1). The geographic distribution of cases of poliomyelitis in

twins corresponds very well with the distribution maps of total cases observed during the 1944 and 1948 epidemics as prepared by the North Carolina State Board of Health (Stevick, 1945, 1950). In each family an attempt was made to examine each member of the sibship including the twins and both parents. Sibs of index twins were followed and examined if possible, even though they had left the original family circle either before or after the occurrence of acute poliomyelitis in the twins. The following information was collected for all available members of the 46 families studied:

1. Pedigree, including collateral relatives closer than second cousins and direct ancestors for all generations where reliable information was available.

2. Clinical data regarding poliomyelitis, including description of any symptoms occurring at or near time of exposure to known cases of poliomyelitis, and all available hospital, clinic or physician's records pertaining to any diagnosed or suspicious illnesses. Information was obtained directly from each individual or his parents within the sibship of the affected twins, but information concerning poliomyelitis in more distant relatives was usually based on history alone.

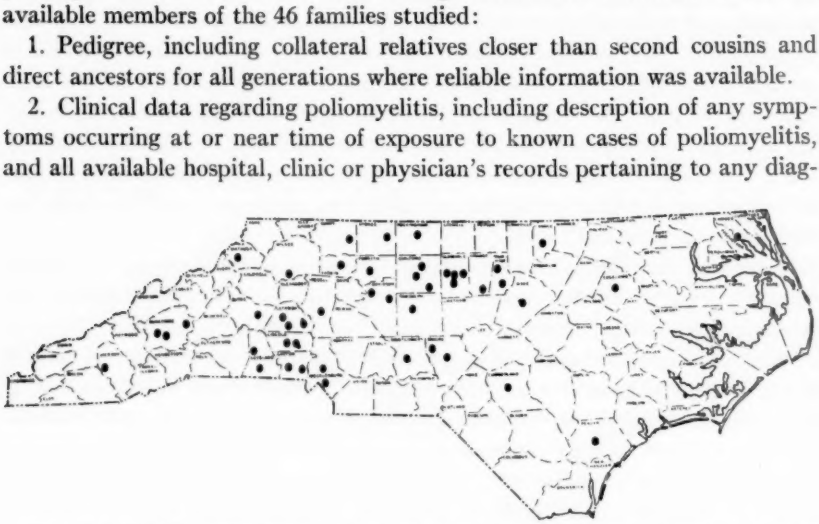

FIGURE 1. North Carolina. Geographic distribution of 46 families each containing a set of twins, one or both having had paralytic poliomyelitis.

3. Blood specimen for determination of ABO blood group, MN blood type, and Rh factor.

4. Saliva specimen for determination of secretor factor.

5. Taste testing with phenyl-thiocarbamide.

6. Palm prints and finger prints.

7. Photographs of twins.

8. Other information gathered but not used in the following analysis included data regarding sanitary facilities and living conditions of families; presence of other known cases of poliomyelitis in the community at time of acute infection in studied family; type of ear lobe and digital hair classification of twins.

For ABO blood grouping reactions, anti-A and anti-B serum prepared by the Blood Bank of Dade County, Miami, Florida, and distributed by the American Hospital Supply Corporation was used. For subdivision of group A bloods into groups A_1 and A_2, anti-A_1 (absorbed B) serum obtained from the Wiener Serum Laboratory, Brooklyn, New York, was used. Serum from the Wiener Serum Laboratory was also used for MN and Rh classification, using anti-M, anti-N, anti-C (anti-Rh′), anti-D (anti-Rh_0) and anti-E (anti-Rh″) sera. A saline suspension of washed cells obtained from the finger-tip was used for all blood determinations, following standard methods of procedure (see Wiener, 1946). The ABO and MN reactions were done in well slides at room temperature and the Rh reactions were done by the test tube method, with incubation for one hour in a water bath at 37°C. The enzymes in the saliva specimens were inactivated promptly after collection by immersing the tubes in a boiling water bath. The salivas were later tested for presence of A or B antigen by incubation with suitably titrated anti-A or anti-B serum, followed by addition of known test cells of the proper blood group. With this technique a secretor classification of persons of blood group O cannot be obtained. Palm and finger prints were obtained by a contact printing method, using sensitized paper obtained from the Faurot Protective Identification System and lightly wiping the hands of the subject with a solution containing tincture of ferric chloride 40%, 80% alcohol 10%, and glycerine 50%. The print develops immediately upon contact of this solution with the sensitized paper.

RESULTS

The information collected from the 46 families studied is summarized below. The case reports abstract information obtained from all sources concerning the illness of the index twin and also any other members of the family with proved or suspected poliomyelitis, whether paralytic or non-paralytic. It will be noted that a definite diagnosis can be made for all index cases and many of the secondary cases, but that all cases that did not present evidence of definite muscle involvement are listed as "abortive poliomyelitis." In some of the latter group a definite diagnosis cannot be made, and the symptoms were such that poliomyelitis would not have been suspected had they not occurred during a poliomyelitis epidemic or in the household of a known case of this disease.

The trait tabulation (table 1) presents data regarding clinical classification and test factors for all members of each family. These data are presented *in extenso* so that further analysis may be undertaken by others if this proves to be desirable. The zygosity diagnosis of the majority of twin pairs may be checked from this table, and further analysis for linkage relations, possible effects of maternal age or birth order could also be made. Because of limitations of space, data on palm and finger prints cannot be published at this time. Dermatoglyphic classification was one of the chief factors in zygosity classification in 19 out of 47 twin pairs. Palm and finger prints are being placed on permanent file in this department, and may be made available for examination on request.

TABLE 1. POLIOMYELITIS STATUS AND TEST FACTOR DATA FOR 47 PAIRS OF TWINS AND THEIR PARENTS AND SIBS

The table gives the classification of index twin cases and their parents and sibs with regard to presence of poliomyelitis, test factors and zygosity diagnosis. Details of the illness of any patient classified as paralytic poliomyelitis (P) or non-paralytic poliomyelitis (p) are given in the case reports. The diagnosis must be regarded as questionable in many of the non-paralytic cases, as the symptoms were frequently such that a diagnosis of poliomyelitis would probably not have been seriously considered had there not been a paralytic case in the family at the same time. Only cases listed as paralytic (P) are considered as "affected" in further analysis of these data. Palm and finger prints were carefully considered in addition to the traits listed in arriving at a diagnosis of zygosity of the twin pairs.

Symbols: P = paralytic poliomyelitis
p = non-paralytic poliomyelitis
n = normal
S = secretor
s = non-secretor
T = taster of PTC
t = non-taster of PTC
— = unknown datum
★ = propositus
d-x = died at x years

A_1, A_2, B, A_1B, A_2B, O = blood group
M, N, MN = blood type
CDE, CDe, etc. = Rh reactions (C, D, E indicate positive reactions to sera anti-C, anti-D, anti-E; c, d, e indicate negative reactions to the same three sera)

FAMILY 1. ★ DZ TWINS

Father	50	n	A_1	M	CDe	s	t
Mother	50	n	O	MN	CDe	—	T
Sister	30	n	O	MN	CDe	—	T
Brother	25	n	O	MN	CDe	—	t
Sister	18	n	O	MN	CDe	—	T
★ Twin (♂)	13	P	O	MN	CDe	—	T
Twin (♀)	13	n	A_1	M	CDe	s	T

FAMILY 2. ★ DZ TWINS

Father	—	n	O	M	CDE	—	T
Mother	—	n	A_1	MN	CDe	—	T
Brother	33	n	O	MN	CDE	—	T
Brother	31	n	O	M	CDE	—	T
Sister	29	n	O	MN	CDe	—	T
Sister	27	n	A_1	M	CDE	S	T
Sister	25	n	A_2	MN	CDe	S	T
[1] Sister	23	n	—	—	—	—	—
Brother	20	n	A_1	MN	CDe	S	T
Sister	17	n	O	M	CDe	—	T
Sister	15	n	A_1	MN	CDe	S	T
★ Twin (♀)	11	P	O	MN	CDE	—	T
Twin (♀)	11	n	A_1	MN	CDE	S	T
Sister	4	n	O	M	CDE	—	T

[1] Not examined.

FAMILY 3. ★ MZ TWINS

Father	35	n	A_1	M	cDE	s	T
Mother	29	n	B	—	Cde	S	T
Brother	12	p	O	—	cde	—	T
Sister	9	n	O	—	cde	—	T
★ Twin (♀)	7	P	O	—	cde	—	T
★ Twin (♀)	7	P	O	—	cde	—	T
Sister	4	n	A_1	—	Cde	S	T

FAMILY 4. ★ DZ TWINS

[1] Father	*d*-47	n	—	—	—	—	—
Mother	44	n	O	MN	cDE	—	T
Brother	26	n	A_1	MN	cde	S	T
Brother	23	n	A_1	N	cDE	S	T
Brother	20	n	A_1	N	cDE	S	T
Sister	17	n	O	MN	cde	—	T
★ Twin (♀)	14	P	O	M	CDe	—	T
Twin (♀)	14	n	A_1	MN	cde	—	T
Sister	11	n	A_1	N	CDE	—	T
[2] Brother	9	n	—	—	—	—	—

[1] Deceased April 23, 1949.
[2] Not examined.

TABLE 1.—*Continued*

FAMILY 5. ★ DZ TWINS

Father	29	n	A_1	MN	CDe	S	t
Mother	29	n	A_1	MN	CDe	S	T
Brother	6	n	O	N	CDe	—	T
★[1] Triplet (♂)	2	P	A_1	MN	CDe	S	T
Triplet (♀)	2	n	A_1	MN	CDe	S	T
Triplet (♀)	2	n	A_1	MN	CDe	S	T

[1] Two-ovum triplets, classed as two dizygous twin pairs.

FAMILY 6. ★ DZ TWINS

Father	36	n	O	M	cDe	—	T
Mother	29	n	O	M	cde	—	T
Sister	10	n	O	M	cde	—	T
★ Twin (♂)	8	P	O	M	cDe	—	T
Twin (♂)	8	p	O	M	cDe	—	T

FAMILY 7. ★ MZ TWINS

Father	30	n	A_1	M	CDe	S	T
Mother	28	n	B	M	CDe	S	T
Sister	11	n	B	M	CDe	S	T
Brother	9	n	A_1B	M	CDe	—	T
★ Twin (♂)	8	P	A_1	M	CDe	S	T
Twin (♂)	8	n	A_1	M	CDe	S	T
[1] Brother	2	n	A_1B	M	cde	—	—

[1] Born since onset polio in twins.

FAMILY 8. ★ DZ TWINS

Father	30	n	O	N	CDe	—	t
Mother	29	n	A_2	N	cdE	S	T
[1] Brother	10	n	—	—	—	—	—
★ Twin (♀)	7	P	A_2	N	cde	S	t
Twin (♂)	7	n	A_2	N	CDE	S	t
Brother	5	n	A_2	N	cde	s	?
[2] Brother	1	n	O	N	CDe	—	?

[1] Not examined.
[2] Age 6 weeks when sister had polio.

FAMILY 9. ★ DZ TWINS

Father	37	n	A_1	MN	cDE	s	t
Mother	39	n	A	N	CDe	S	t
★ Twin (♂)	6	P	A_1	N	CDe	s	?
★ Twin (♀)	6	P	A_1	N	cDE	s	t
Brother	8	p	O	N	cde	—	t

FAMILY 10. ★ DZ TWINS

Father	36	n	O	M	CDe	—	T
Mother	33	n	O	N	Cde	—	T
★ Twin (♂)	9	P	O	MN	Cde	—	T
Twin (♂)	9	n	O	MN	Cde	—	T
Half-brother	15	n	A_1	MN	cde	S	T
[1] Half-sister	13	n	A_1	N	cde	S	T

[1] Not living with family.

FAMILY 11. ★ DZ TWINS

Father	28	n	A_1	MN	CDe	—	—
Mother	27	n	A_2	MN	CDe	—	—
[1] Sister	9	n	—	—	—	—	—
[2] Brother	7	P	A_1	MN	CDe	—	—
[3] Brother	5	P	O	MN	CDe	—	—
[1] Sister	4	n	—	—	—	—	—
[2] Twin (♂)	2	P	A_1	MN	CDe	—	—
Twin (♀)	2	n	O	M	CDe	—	—

[1] Blood specimen not obtained.
[2] 1948 epidemic.
[3] 1944 epidemic.

FAMILY 12. ★ MZ TWINS

Father	42	n	A_1	MN	CDe	S	T
Mother	40	n	O	M	cde	—	T
★ Twin (♂)	8	P	A_1	MN	cde	S	T
Twin (♂)	8	n	A_1	MN	cde	S	T
Sister	3	n	A_1	M	cde	S	T

FAMILY 13. ★ DZ TWINS

Father	26	n	O	N	CDe	—	T
Mother	24	n	A_1	M	CDE	S	T
Sister	3	n	A_1	MN	cDE	S	t
★ Twin (♂)	2	P	A_1	MN	cDE	s	?
Twin (♀)	2	n	A_1	MN	CDe	s	?

FAMILY 14. ★ MZ TWINS

Father	32	n	O	MN	cde	—	t
Mother	28	n	O	MN	cDE	—	T
★ Twin (♀)	9	P	O	N	cDE	—	T
Twin (♀)	9	p	O	N	cDE	—	T
[1] Twin (♀)	6	n	O	N	cDE	—	T
[1] Twin (♀)	6	n	O	N	cDE	—	T

[1] Born since polio attack in 1st set of twins.

TABLE 1.—*Continued*

FAMILY 15. ★ MZ TWINS

[1] Father	*d*-43	n	—	—	—	—	—
Mother	46	n	O	MN	cDE	—	t
★ Twin (♂)	9	P	O	MN	CDE	—	t
★ Twin (♂)	9	P	O	MN	CDE	—	t

[1] Deceased.

FAMILY 16. ★ DZ TWINS

Father	31	n	A_1	M	CDe	S	T
Mother	35	n	O	MN	cde	—	T
Sister	9	p	O	M	cde	—	—
Brother	8	p	O	M	CDe	—	T
Sister	7	n	A_1	M	cde	S	T
★ Twin (♀)	5	P	A_1	MN	CDe	S	t
Twin (♀)	5	n	A_1	MN	CDe	S	t
Sister	4	n	O	M	cde	—	t
[1] Brother	1	n	O	MN	cde	—	?

[1] Born since polio in siblings.

FAMILY 17. ★ DZ TWINS

Father	53	n	O	MN	Cde	—	T
Mother	47	n	A_1	MN	CDe	s	t
Brother	17	n	A_1	MN	CDe	S	t
Sister	14	n	A_1	M	CDe	S	t
★ Twin (♂)	10	P	O	MN	CDe	—	t
Twin (♀)	10	n	A_1	N	Cde	s	t

FAMILY 18. ★ DZ TWINS

Father	40	n	O	MN	CDe	—	t
Mother	40	n	A_1	MN	CDe	s	T
Sister	11	n	A_1	M	CDe	S	T
Sister	9	P	O	MN	cde	—	T
★ Twin (♂)	4	P	O	N	CDe	—	t
Twin (♀)	4	n	A_1	MN	CDe	s	T

FAMILY 19. ★ DZ TWINS

Father	59	n	O	N	cdE	—	T
Mother	56	n	O	M	CDE	—	T
[1] Sister	*d*-32	n	—	—	—	—	—
Sister	36	n	O	MN	CDE	—	T
Sister	33	n	O	MN	CDE	—	T
Brother	31	n	O	MN	cDE	—	T
Brother	28	n	O	MN	CDE	—	t
Sister	25	n	O	MN	cDE	—	T
Brother	22	n	O	MN	CDE	—	T
★ Twin (♂)	19	P	O	MN	CDe	—	T
Twin (♀)	19	n	O	MN	CDe	—	T
Twin (♂)	16	n	O	MN	CDe	—	T
Twin (♂)	16	n	O	MN	CDE	—	t

[1] Deceased prior to 1948.

FAMILY 20. ★ MZ TWINS

Father	54	n	A_1	MN	CDe	s	T
Mother	52	n	A_1	MN	CDe	S	T
[1] Sister	*d*-3	—	—	—	—	—	—
Brother	31	n	A_1	N	CDe	S	T
Sister	28	n	A_1	MN	CDe	S	T
★ Twin (♂)	18	P	A_1	M	CDe	S	T
★ Twin (♂)	18	P	A_1	M	CDe	S	T

[1] Died of diphtheria.

FAMILY 21. ★ MZ TWINS

Father	50	n	O	N	cde	—	T
Mother	48	n	O	N	cde	—	T
Brother	29	n	O	N	cde	—	T
Sister	28	n	O	N	cde	—	T
Brother	25	n	O	N	cde	—	T
★ Twin (♂)	23	P	O	N	cde	—	T
Twin (♂)	23	n	O	N	cde	—	T
Sister	18	n	O	N	cde	—	T
Sister	14	n	O	N	cde	—	T

FAMILY 22. ★ DZ TWINS

Father	31	n	O	MN	cde	—	T
Mother	25	n	O	M	CDe	—	T
Sister	10	n	O	MN	cde	—	T
Brother	8	n	O	M	cde	—	T
Brother	5	n	O	MN	cde	—	T
★ Twin (♂)	3	P	O	MN	cde	—	T
Twin (♂)	3	n	O	MN	CDe	—	T
Brother	2	P	O	MN	cde	—	?

FAMILY 23. ★ DZ TWINS

[1] Father	39	n	—	—	—	—	—
Mother	37	n	—	—	—	—	—
Brother	16	n	—	—	—	—	—
Brother	14	n	—	—	—	—	—
Sister	5	n	—	—	—	—	—
★ Twin (♂)	*d*-2	P	—	—	—	—	—
Twin (♂)	2	p	—	—	—	—	—

[1] No test factors obtained. Affected twin died of bulbar polio. Parents report children did not look alike, no other information regarding zygosity available.

TABLE 1.—*Continued*

FAMILY 24. ★ DZ TWINS

Father	58	n	O	MN	cDe	—	T
Mother	49	n	A_1	MN	cde	S	T
Brother	25	n	A_1	M	cDe	S	T
★ Twin (♂)	23	P	A_1	MN	cde	S	T
Twin (♀)	23	n	A_1	M	cDe	S	T
Brother	20	n	O	N	cde	—	T

FAMILY 25. ★ MZ TWINS

[1] Father	42	n	—	—	—	—	—
Mother	43	n	—	—	—	—	—
Sister	21	n	—	—	—	—	—
★ Twin (♂)	*d*-10	P	—	—	—	—	—
★ Twin (♂)	*d*-10	P	—	—	—	—	—

[1] No test factors obtained, both twins died of bulbar polio. Said by parents and neighbors to have been indistinguishable. One was left-handed, other right-handed. Photos examined, appear identical.

FAMILY 26. ★ DZ TWINS

[1] Father	—	—	—	—	—	—	—
Mother	47	n	O	N	CDe	—	T
Twin (♂)	19	P	O	MN	cDE	—	T
Twin (♀)	19	n	O	MN	CDE	—	T

[1] Not examined.

FAMILY 27. ★ DZ TWINS

Father	49	n	A_1	N	CDe	S	T
Mother	45	n	O	MN	CDe	—	T
[1] Brother	*d*-23	n	—	—	—	—	—
Sister	26	n	A_1	N	CDe	s	T
[2] Sister	*d*-5	—	—	—	—	—	—
Brother	23	n	A_1	MN	CDe	s	T
Sister	20	n	A_1	N	CDe	s	T
Brother	18	n	O	MN	Cde	—	T
Brother	11	n	O	MN	Cde	—	T
Sister	9	n	A_1	N	Cde	s	T
Sister	8	n	O	MN	Cde	—	T
Brother	6	n	O	MN	Cde	—	T
Sister	5	n	O	N	Cde	—	T
Sister	4	n	O	N	Cde	—	?
★ Twin (♀)	2	P	A_1	N	Cde	s	?
Twin (♂)	2	n	A_1	N	Cde	S	?

[1] Killed in action, U. S. Army.
[2] Died of pneumonia.

FAMILY 28. ★ DZ TWINS

Father	51	n	A_1	MN	CDe	S	T
Mother	46	n	O	MN	cdE	—	T
[1] Sister	*d*-inf.	—	—	—	—	—	—
[2] Brother	28	n	—	—	—	—	—
Sister	26	n	O	MN	cde	—	T
★ Twin (♂)	23	P	A_1	M	cdE	—	T
Twin (♂)	23	n	A_1	MN	CDe	—	T
Brother	19	n	O	N	cdE	—	T
Twin (♂)	17	n	O	N	cdE	—	T
[3] Twin (♂)	*d*-inf.	—	—	—	—	—	—
[3] Sister	*d*-inf.	—	—	—	—	—	—
Sister	15	n	O	MN	CDe	—	T
Sister	12	n	O	M	cdE	—	T
Sister	10	n	O	M	cdE	—	T
Brother	8	n	O	MN	cde	—	T

[1] Died, age 5 days.
[2] Not examined, in U. S. Army.
[3] Died of "colitis" in infancy.

FAMILY 29. ★ MZ TWINS

Father	35	n	A_1	MN	?	s	T
Mother	24	n	O	MN	Cde	—	T
Brother	8	p	A_1	N	CDe	s	T
★ Twin (♀)	6	P	A_1	MN	CDe	s	T
Twin (♀)	6	n	A_1	MN	CDe	s	T
Sister	4	p	A_2	M	CDe	s	?

FAMILY 30. ★ MZ TWINS

Father	38	n	O	MN	cde	—	T
Mother	29	n	A_1	M	CDe	S	t
Sister	10	n	O	MN	CDe	—	T
Sister	8	n	O	M	CDe	—	T
Brother	5	n	A_1	M	CDe	S	T
★ Twin (♀)	3	P	O	MN	cde	—	T
Twin (♀)	3	n	O	MN	cde	—	T

FAMILY 31. ★ MZ TWINS

Father	50	n	O	N	CDe	—	T
Mother	40	n	O	M	CDe	—	T
Brother	19	n	O	MN	CDe	—	T
Sister	17	n	O	MN	CDe	—	T
Brother	14	n	O	MN	CDe	—	T
[1] Sister	12	P	O	MN	CDe	—	T
★[1] Twin (♀)	10	P	O	MN	CDe	—	T
Twin (♀)	10	n	O	MN	CDe	—	T
Brother	7	n	O	MN	CDe	—	T
[2] Sister	5	P	O	MN	CDe	—	T
Brother	3	n	O	MN	CDe	—	T
Brother	2	n	O	MN	CDe	—	?

[1] 1944 epidemic.
[2] 1948 epidemic.

TABLE 1.—*Continued*

FAMILY 32. ★ DZ TWINS							
[1] Father	*d*-62	—	—	—	—	—	—
Mother	60	n	B	M	cDe	S	T
Brother	35	n	A_1B	MN	cDe	S	T
Brother	32	n	B	MN	CDe	S	T
Brother	27	n	B	M	cde	S	T
[2] Brother	25	n	—	—	—	—	—
Sister	21	n	B	MN	CDe	S	T
Brother	17	n	A_1	M	cDe	S	T
Brother	15	n	O	MN	cde	—	T
Twin (♂)	12	P	A_1B	MN	CDe	S	T
Twin (♂)	12	p	A_1	MN	CDe	S	T

[1] Deceased 1938.
[2] Not examined.

FAMILY 33. ★ MZ TWINS							
Father	36	n	O	MN	CDe	—	t
Mother	33	n	O	MN	cde	—	T
Sister	13	n	O	MN	cDe	—	T
Brother	12	n	O	MN	cDe	—	T
Sister	8	n	O	MN	cde	—	T
★ Twin (♂)	7	P	O	MN	cDe	—	t
Twin (♂)	7	n	O	MN	cDe	—	t

FAMILY 34. ★ DZ TWINS							
Father	50	n	A_1	M	CDe	S	T
Mother	43	n	O	MN	cDE	—	T
[1] Sister	25	n	—	—	—	—	—
Brother	24	n	A_2	MN	cDe	S	t
[1] Sister	22	n	—	—	—	—	—
Brother	21	n	A_2	M	cDE	S	t
Sister	19	n	A_2	MN	CDE	S	T
Brother	17	n	A_1	M	cDE	S	T
Brother	15	n	A_1	M	cDE	S	T
Brother	13	p	A_1	M	cDE	S	T
Sister	11	n	A_1	M	cDE	S	T
★ Twin (♂)	8	P	A_1	MN	cDE	S	t
Twin (♂)	8	p	A_1	MN	CDe	S	T
Sister	2	n	A_1	M	cDe	S	?

[1] Not examined.

FAMILY 35. ★ DZ TWINS							
Father	43	n	O	N	Cde	—	T
Mother	40	n	O	MN	Cde	—	T
[1] Brother	23	n	—	—	—	—	—
[2] Brother	*d*-11	—	—	—	—	—	—
[1] Brother	21	n	—	—	—	—	—
Sister	19	p	O	MN	Cde	—	T
Brother	15	n	O	N	Cde	—	T
Sister	11	n	O	N	Cde	—	T
Brother	9	n	O	MN	Cde	—	T
Brother	5	n	O	N	Cde	—	T
★ Twin (♂)	2	P	O	MN	Cde	—	T
Twin (♂)	2	n	O	N	Cde	—	T

[1] Not examined.
[2] Deceased "heart trouble."

FAMILY 36. ★ DZ TWINS							
Father	45	n	O	M	CDE	—	T
Mother	40	n	A_1	MN	CDE	S	T
[1] Brother		—	—	—	—	—	—
Sister	9	n	A_1	MN	CDE	S	T
★ Twin (♀)	8	P	O	M	CDE	—	T
Twin (♀)	8	n	A_1	MN	CDE	S	T
[1] Sister		—	—	—	—	—	—
Brother	6	n	O	MN	CDE	—	T
Sister	4	n	A_1	MN	CDE	S	T
Sister	2	n	A_1	M	CDE	S	?
[1] Twin (♂)		—	—	—	—	—	—
[1] Twin (♂)		—	—	—	—	—	—

[1] Stillborn.

FAMILY 37. ★ DZ TWINS							
Father	48	n	A_1	MN	cDE	S	t
Mother	44	n	A_2	MN	CDe	s	T
Brother	24	n	A_1	M	CDE	S	t
Brother	23	n	A_1	N	cdE	S	—
Sister	20	n	A_2	MN	CDE	S	T
[1] Brother	18	n	—	—	—	—	—
[2] Brother	*d*-2	—	—	—	—	—	—
Twin (♂)	11	P	A_1	MN	CDE	S	t
Twin (♂)	11	n	A_1	MN	CDE	S	t

[1] Not examined.
[2] Deceased, cause unknown.

FAMILY 38. ★ DZ TWINS							
Father	39	n	B	MN	CDe	S	T
Mother	29	n	O	N	CDe	—	t
Brother	6	n	O	MN	CDe	—	t
★ Twin (♀)	4	P	B	N	Cde	S	t
Twin (♀)	4	n	B	N	CDe	S	t

FAMILY 39. ★ DZ TWINS							
Father	51	n	O	N	cDE	—	T
Mother	47	n	A_2	MN	cDE	S	T
Sister	22	n	A_2	N	cDE	S	T
Brother	20	n	A_2	MN	cDE	S	T
Sister	17	n	A_2	MN	cDE	S	T
★ Twin (♂)	15	P	A_2	N	cDE	S	T
Twin (♂)	15	n	A_2	MN	cde	S	T
Brother	10	n	A_2	MN	cde	s	t

TABLE 1.—*Continued*

FAMILY 40. ★ DZ TWINS

Father	35	n	A_1B	MN	cde	S	T
Mother	35	n	O	M	cDe	—	T
Brother	10	n	A_1	MN	cde	S	T
Sister	8	n	A_1	M	cde	S	T
Brother	5	n	B	M	cde	s	T
★ Twin (♀)	3	P	B	M	cDe	S	T
Twin (♂)	3	n	B	M	cde	s	T

FAMILY 41. ★ MZ TWINS

Father	39	n	O	M	cde	—	T
Mother	37	n	O	MN	cDe	—	T
Brother	17	n	O	MN	cde	—	T
[1] Brother	*d*-2	—	—	—	—	—	—
Sister	14	n	O	MN	cde	—	T
Sister	10	n	O	MN	cde	—	T
★ Twin (♂)	5	P	O	M	cde	—	t
Twin (♂)	5	n	O	M	cde	—	t

[1] Deceased of whooping cough and pneumonia.

FAMILY 42. ★ DZ TWINS

Father	35	n	O	N	cde	—	t
Mother	29	n	O	N	CDE	—	T
Half-brother	13	n	B	MN	cDE	s	T
Half-sister	10	n	O	MN	cDE	—	T
★ Twin (♀)	2	P	O	N	Cde	—	?
Twin (♀)	2	n	O	N	cDE	—	?
[1] Twin (♀)	1	—	O	N	cDE	—	?
Twin (♂)	1	—	O	N	cDe	—	?

[1] Born since onset of polio in index case.

FAMILY 43. ★ MZ TWINS

Father	36	n	A_2	MN	CDe	S	t
Mother	30	n	B	MN	cde	s	T
Sister	15	n	A_2	N	CDe	S	t
Sister	13	n	B	N	CDe	s	t
Brother	8	n	O	M	cde	—	T
Sister	5	n	O	M	cde	—	t
★ Twin (♀)	3	P	O	MN	cde	—	?
★ Twin (♀)	3	P	O	MN	cde	—	?

FAMILY 44. ★ DZ TWINS

Father	27	n	A_1	N	CDe	S	T
Mother	25	n	A_1	N	CDe	s	T
Sister	6	n	O	N	CDe	—	t
★ Twin (♀)	2	P	O	N	CDe	—	?
Twin (♀)	2	n	A_1	N	CDe	s	?

FAMILY 45. ★ DZ TWINS

Father	29	n	O	MN	cDe	—	t
Mother	29	n	O	MN	CDe	—	T
Brother	10	P	O	MN	CDe	—	T
Sister	8	n	O	MN	CDe	—	T
★ Twin (♂)	6	P	O	MN	CDe	—	T
★ Twin (♂)	6	P	O	MN	CDe	—	?

FAMILY 46. ★ DZ TWINS

[1] Twin (♂)	3	P	O	MN	CDe	—	?
Twin (♂)	3	p	A_1	MN	CDe	S	?

[1] Twins adopted, parents unknown.

CASE REPORTS

FAMILY 1. Twin, white male, born Oct. 17, 1946, On Sept. 11, 1947, a "boil" appeared on the patient's neck. During home treatment there was moderate fever, mild frontal headache and pain at the site of infection. On Sept. 18 severe pain appeared involving the left arm and shoulder with radiation into the neck, although the "boil" appeared to be healing. Paralysis of the left upper extremity appeared within 24 hours. On admission to the N. C. Baptist Hosp., Winston-Salem, N. C. on Sept. 29, he presented flaccid paralysis of the left deltoid and the extensor and rotator muscles of the left shoulder, with some muscle atrophy in this region, and moderate weakness of the left hand. Although the spinal fluid was within normal limits, a diagnosis of sequelae of poliomyelitis was made and he was treated with hot packs and physiotherapy. He was discharged on Oct. 8 and physiotherapy continued. Weakness gradually improved, and full function of the affected muscles was regained within a few months.

FAMILY 2. Twin, white female, born Apr. 29, 1948. On July 15, 1948 she was stung on the lip by a hornet. Within an hour she complained of pain and stiffness of the legs and back.

On the following day there was weakness of the legs, rapidly progressive until she was unable to stand. She was admitted to the Biltmore Orthopedic Home, Asheville, N. C. on July 17. There was moderate pharyngitis, stiffness and spasm of the neck and back, and flaccid paralysis of the lower extremities. The temperature rose to 104° and the white count on July 19 was 17,300. Lumbar puncture was not done. She received physiotherapy until discharged on Oct. 5 with bilateral leg braces, with almost complete paralysis of both lower extremities. She was readmitted from Nov. 26, 1948 until July 10, 1949 for further physiotherapy, and was able to walk with leg braces and crutches on discharge.

FAMILY 3. *Case A.* Twin, white female, born March 2, 1942. On July 2, 1948 she complained of severe headache. Sore throat and fever appeared that evening and she was quite restless for several days. On July 7 she did not want to stand up. On July 8 she began vomiting and complained of pain in the right leg and paralysis of this leg appeared. A lumbar puncture was reported as "typical of poliomyelitis" but the original data are not available. She was referred to the Emergency Poliomyelitis Hosp., Greensboro, N. C. where weakness of the neck muscles and paralysis of the right leg were noted. After four weeks treatment she was transferred to a convalescent center for three months. On May 17, 1949 there was marked residual weakness of the right leg and she walked with a limp.

Case B. Twin, white female, born March 2, 1942. On July 10, 1948 there was sore throat and moderate fever. On the following day pain and aching of both legs appeared, with marked weakness and inability to walk. The family physician made a diagnosis of "acute poliomyelitis", but no laboratory work was done. She was treated at home and regained use of her lower extremities within 10 days, with no residua demonstrable.

Case C. Brother, white male, born Feb. 28, 1947. On July 17, 1948 he complained of headache and pain in the legs, and had mild fever. He was improved on the following day and made an uneventful recovery.

FAMILY 4. Twin, white female, born March 31, 1935. During March 1947 she developed a sore throat and mild fever and was thought to have tonsillitis. Fever lasted about one week, then pain and spasm of the back muscles and left shoulder and arm appeared. The family physician made a diagnosis of "neuritis and tonsillitis." Muscle pain continued for about two weeks, somewhat relieved by local heat. Drooping of the left shoulder was noted. On recovery from the acute attack it was found that scoliosis had appeared, and she was admitted to the N. C. Orthopedic Hosp., Gastonia, N. C. on July 13, 1948 where a diagnosis of post-paralytic severe scoliosis, resulting from poliomyelitis, was made. Treatment designed to straighten the spine was administered, including a turnbuckle correction cast, physiotherapy and Risser jacket. Spinal fusion operations were done in Sept. and Oct. 1948. She was discharged Dec. 5, 1948. In Sept., 1949 she was still wearing a body jacket and the spinal correction was holding in a satisfactory manner.

FAMILY 5. Triplet, white male, born Dec. 31, 1946. On Sept. 9, 1948 he became ill with fever and vomiting, and was very drowsy and irritable. A lumbar puncture done at the Catawba General Hosp., Newton, N. C. showed a bloody tap, but the centrifuged supernatant fluid gave a positive Pandy reaction. On Sept. 11 he was referred to the N. C. Orthopedic Hosp., where he was found to have a stiff neck, pharyngitis, weakness of the left leg and abdominal muscles, and spasm of shoulder muscles. Recovery was uneventful and he was discharged Sept. 17. No residual paralysis was demonstrable on a clinic visit on Sept. 28, 1948 and he was healthy when examined on July 15, 1949.

FAMILY 6. *Case A*. Twin, white male, born Apr. 6, 1941. On about Sept. 1, 1948 he developed a "cold and sore throat" and had fever of 102°F. The family physician made a diagnosis of tonsillitis and a sulfa drug was administered for several days. On Sept. 5 he fell down several times while playing. That night he complained of pain in the back of the neck. On Sept. 6 he was unable to sit up because of pain and headache. Penicillin was given for 3 days with reduction of fever. On Sept. 12 there was severe pain in both lower extremities and weakness of the right upper and lower extremities. On admission to the James Walker Memorial Hosp., Wilmington, N. C. on Sept. 15, 1948 there was stiffness of the neck and back, spasm of the right hamstring muscles, and weakness of the right arm and leg. Spinal fluid showed a cell count of 30 and positive Pandy. He was treated with hot packs and muscle reeducation. On Sept. 21 there was still generalized weakness of the right upper extremity. There was only slight weakness when discharged on Sept. 29, and muscle power was gradually regained. When examined on July 5, 1949 there was no evidence of residual paralysis.

Case B. Twin, white male, born April 6, 1941. During Sept., 1948 at the time of illness of his twin, this child also developed a "cold and sore throat" and had fever. He was given a sulfa drug and symptoms subsided after about 3 days. He had recovered by the time paralysis appeared in his twin.

FAMILY 7. Twin, white male, born July 4, 1941. On Aug. 10, 1943 there was fever and restlessness, and he would cry when lifted or moved. On Aug. 13 there was stiffness of the neck and he was unable to stand alone. He was admitted to Duke University Hosp., Durham, N. C. on Aug. 14 presenting flaccid paralysis of the entire left lower extremity, with tenderness and pain on motion. The spinal fluid contained 86 cells (81 mononuclear and 5 polymorphonuclear), Pandy negative, culture negative and sugar normal. A diagnosis of acute anterior poliomyelitis was made and he was treated with prostigmine, warm packs and physiotherapy, with slight improvement of muscle function. He was transferred to the N. C. Orthopedic Hosp. on Sept. 14 presenting almost complete flaccid paralysis of the entire left lower extremity and mild involvement of the right thigh and abdominal muscles. Treatment continued with gradual improvement and he was discharged on March 12, 1944, able to walk with a single leg brace. He was followed in a clinic at intervals and was relatively unchanged on Sept. 6, 1949 when he presented marked muscle atrophy of the left lower extremity with a flail foot.

FAMILY 8. Twin, white female, born July 9, 1942. On May 24, 1948 she staggered in walking and seemed to have weakness of the legs. On May 25 she was unable to stand and there was mild fever. Lumbar puncture done at Pittman Hosp., Fayetteville, N. C. was reported as "positive." She was referred to the N. C. Orthopedic Hosp. on May 27 and had become rapidly worse, being semi-comatose and unable to speak or swallow. The gag reflex was absent. Respiration seemed adequate but only the lower intercostals were functioning. Both lower extremities and the left upper extremity were paralyzed. A diagnosis of acute bulbar poliomyelitis was made, and supportive treatment included oxygen and pharyngeal suction. By May 29 she could speak clearly and she became able to swallow on the following day. By June 4 no paralysis could be detected, and she was discharged June 7 and followed in the clinic. On July 7, 1949 there was no evidence of residual paralysis.

FAMILY 9. *Case A*, Twin, white male, born Aug. 14, 1943. On July 3, 1948 there was fever of 103°F. and headache. Temperature returned to normal July 5, but fever recurred July 7

and weakness of both left extremities appeared. On admission to Charlotte Memorial Hosp. on July 8 there was marked weakness of the abdominal and left thigh muscles, and moderate weakness of muscles about the right hip. Spinal fluid contained 450 cells. He was treated with hot packs and exercise in the Hubbard tank. Fever subsided by July 12 and muscle function showed gradual improvement. He was discharged Oct. 10, still showing weakness of the left hip and back, and using a brace and crutches. Physiotherapy was continued, and crutches were discarded Jan. 25, 1949. On May 10, 1949 there was still definite weakness of the muscles about the left hip and left shoulder and the abdominal muscles.

Case B. Twin, white female, born Aug. 14, 1943. On July 3, 1948 this child also developed fever and headache. Fever subsided July 6 but recurred for one day July 10. On July 13 she again had fever, sore throat, stiff neck and pain in the legs. On admission to Charlotte Memorial Hosp. on July 14 the spinal fluid showed "cells present" and positive Pandy. There was rigidity and tenderness of the neck and spasm of the hamstring muscles. She was treated with hot packs and was discharged July 22 with slight residual weakness of the right thigh, but the weakness was not detectable two weeks later. On May 10, 1949 no residual signs were found.

Case C. Brother, born Feb. 3, 1941. This child developed fever on the day following onset of illness in the twins. Low grade fever persisted several days and there was headache and questionable stiffness of the neck. No muscle weakness was detected, and lumbar puncture was not done. He recovered completely within three weeks.

FAMILY 10. Twin, white male, born Nov. 6, 1940. During Sept., 1948 he had fever and headache for two or three days, then seemed well for four or five days. On Sept. 20 he complained of headache and severe pain in the shoulders and neck, and had fever. He was admitted to the City Memorial Hosp., Winston-Salem, N. C. on Sept. 21 presenting stiff neck and weakness about the shoulder girdle. Spinal fluid: cell count 276, polymorphonuclears 43%, lymphocytes 57%; sugar 80 mgms.; chlorides 470 mgms.; Pandy trace. He was treated with hot packs and fever subsided in 4 days. Weakness of the neck and shoulders disappeared by Sept. 30. He was discharged Oct. 8 with no residual signs. On June 8, 1949 no muscle weakness was demonstrated, but the mother stated that he tired more easily than other children.

FAMILY 11. *Case A.* Twin, white male, born June 19, 1947. One week before the acute illness there was an episode of mild diarrhea. His brother (see Case B) became ill with poliomyelitis July 23, 1948. On July 25 he developed fever, restlessness and vomiting. The following morning he screamed if touched and made no attempt to walk or crawl. On admission to the N. C. Baptist Hosp. July 26, temperature was 102°F. and there was stiffness of the neck. Spinal fluid: cell count 180, 20% polymorphonuclears, 80% mononuclears; protein 61 mgms.; sugar 70 mgms.; culture negative. There was weakness of both left extremities. He responded promptly to routine treatment and was discharged Aug. 5 with no evidence of residual paralysis. On return to the clinic Aug. 20 weakness of the left leg was found. On Sept. 23 he walked with a left limp and stumbled frequently. On Nov. 30 the left thigh measured ½ inch less in diameter than the right and weakness of the quadriceps muscle was demonstrated. Improvement was noted Feb. 22, 1949 and a barely perceptible limp was present on Apr. 21.

Case B. Brother, white male, born Oct. 20, 1941. On July 23, 1948 there was fever, headache and stiffness of the neck. He was admitted to the N. C. Baptist Hosp. on July 24 presenting marked rigidity of the neck and back and weakness of muscles about the right hip and thigh. Temperature 101.6°F. Spinal fluid: cell count 215, 8% polymorphonuclears,

92% mononuclears; sugar 20 mgms.; chlorides 680 mgms.; Pandy neg.; culture neg. Moderate weakness of the right leg was present on discharge Aug. 6. Weakness had disappeared by Apr. 21, 1949.

Case C. Brother, white male, born Dec. 3, 1943. On Aug. 11, 1944 he developed fever and sore throat. Five days later spasm of the extremities and neck appeared. The family physician made a diagnosis of poliomyelitis and he was referred to the Emergency Poliomyelitis Hosp., Hickory, N. C. Record of the spinal fluid examination is not available. He remained under treatment for 8 weeks, and on discharge had partial paralysis of the right leg and was unable to walk. He was admitted to the Charlotte Memorial Hosp. from May 1, 1946 until Oct. 30, being given physiotherapy and stretching of the right Achilles tendon, and he was taught to walk with crutches. Leg braces were later added and he was soon able to discard the crutches. Braces were removed during the summer of 1948. On Apr. 21, 1949 there was still deformity of the right foot and a tendon transplant operation was recommended.

FAMILY 12. Twin, white male, born June 17, 1941. On Sept. 23, 1948 he became ill with fever and headache. On the following day there was stiffness of the neck and vomiting. He was admitted to the Biltmore Orthopedic Home on Sept. 27 presenting stiffness of the neck and leg muscles. Spinal fluid: cell count 1,080, predominantly lymphocytes, Pandy positive. Temperature was 103°F. on admission, gradually subsiding within a week. He was discharged on Oct. 8 showing weakness of the abdominal muscles. No residual signs were present on July 26, 1949.

FAMILY 13. Twin, white male, born Aug. 15, 1947. On Aug. 22, 1948 he appeared to be ill. By Aug. 24 he was unable to crawl and dragged the right leg, and temperature was 101°F. On admission to the N. C. Orthopedic Hosp. Aug. 25 there was rigidity of the neck and paralysis of muscles about the right hip. Spinal fluid: cell count 265, predominantly lymphocytes; Pandy positive. On Sept. 7 there was no function of the right toe extensors, tibial and peroneal muscles, and a cast was applied. The cast was removed Sept. 20, improvement of the peroneals was noted and a splint was applied. Orthopedic treatment was continued on an out-patient basis with gradual improvement. On Aug. 9, 1949 he was able to walk with a leg brace, but there was residual paralysis of the right quadriceps and tibial muscles and marked equinovalgus deformity of the foot.

FAMILY 14. *Case A.* Twin, white female, born Aug. 20, 1940. During July, 1941 she suddenly became ill with high fever and vomiting. Three days later the back became weak, and she was unable to sit up or use the left arm or leg. A diagnosis of acute poliomyelitis was made by the family physician and she was treated at home. Upon recovery from the acute phase, she was referred to the N. C. Orthopedic Hosp., being seen in clinic Aug. 26, 1941. The deltoid muscles bilaterally were severely affected and there was flexion contracture of the left knee. With physiotherapy and braces, gradual improvement occurred. By Feb. 8, 1944 abduction of the left arm was practically normal and the brace was discontinued. On July 31, 1945 it was noted that a full range of voluntary motion was possible at both shoulders, but there was severe atrophy of muscles about the shoulders, especially the supraspinatus and infraspinatus. On Aug. 1, 1949 there was definite weakness of the left arm and moderate atrophy about the shoulder girdle.

Case B. Twin, white female, born Aug. 20, 1940. Two days after onset of poliomyelitis in her twin, she had high fever for two or three days, then recovered. No muscle paralysis was noted.

FAMILY 15. *Case A.* Twin, white male, born Nov. 21, 1941. On July 24, 1948 there was headache and fever of 101°F. Fever subsided for two days, then recurred July 27 associated with sore throat and irregular breathing. He was referred to the Central Carolina Convalescent Hosp., Greensboro, N. C. on July 28 presenting pharyngitis, moderate stiffness of the neck, and tightness of the back and hamstring muscles. Spinal fluid: cell count 215, 70% lymphocytes, Pandy positive. He became stuporous, bulbar signs appeared and a tracheotomy was done July 29. He improved gradually and the tracheotomy tube was removed Aug. 25. Convalescence was complicated by aspiration pneumonia beginning Aug. 31, but responding quickly to treatment. When discharged on Nov. 17 he presented weakness of the anterior neck muscles, mild facial involvement, and mild weakness of muscles of the pelvic girdle.

Case B. Twin, white male, born Nov. 21, 1941. On July 31, 1948 he developed fever and vomiting began on the following day. On Aug. 2 there was pain and weakness of the neck, difficulty in swallowing appeared that night, and he was admitted to the Central Carolina Convalescent Hosp. on Aug. 3. Temperature was 103.6°F.; there was weakness of the right facial muscles and the left side of the palate, and marked tightness of the neck, back and hamstring muscles. Lumbar puncture was not done. He was unable to swallow on Aug. 4 and was fed by gavage and intravenously until Aug. 16 when he became able to swallow liquids. When discharged on Nov. 17 he presented weakness and slight atrophy of the left quadriceps muscle.

FAMILY 16. *Case A.* Twin, white female, born Feb. 5, 1944. On July 21, 1948 she became fretful, complained of pain in the neck and headache and would not attempt to walk. There seemed to be generalized muscle pain, as she complained of tenderness wherever touched. On the following day there was nausea and vomiting and the neck was "drawn over" to the right side. A lumbar puncture was done and the fluid was reported to be "positive for poliomyelitis," but details are not available. She was referred to Rex Hosp., Raleigh, N. C. on July 23 presenting stiffness and weakness of the neck muscles and both thighs. She improved rapidly and was discharged without residua on Aug. 6.

Case B. Brother, born Aug. 1, 1941. This child developed high fever and headache two days before onset of poliomyelitis in Case A, but recovered spontaneously within a week with no paralysis being noted.

Case C. Sister, born Apr. 30, 1940. On the day after onset of poliomyelitis in Case A she developed fever, sore throat, headache and severe pain in the legs. Although the parents report that there was weakness of the legs for about 4 days, reliable medical observation are not available. She recovered on home treatment in about one week with no evidence of residua. Classed as non-paralytic.

FAMILY 17. Twin, white male, born June 29, 1939. On July 14, 1948 he developed severe headache and fever, and became delirious that night. The family physician found a stiff neck and spasm of the left arm and both legs. He was admitted to Watts Hosp., Durham, N. C. on July 15 presenting in addition weakness of the flexor muscles of the left hand. Spinal fluid: cell count 16 lymphocytes. Temperature returned to normal July 22 and he was discharged. No residual signs were noted Aug. 25, 1949.

FAMILY 18. *Case A.* Twin, white male born Apr. 7, 1945. On June 21, 1948 he developed fever and nuccal pain. On admission to the N. C. Orthopedic Hosp. June 24 there was rigidity of the neck and tightness of the hamstring muscles. Spinal fluid: cell count 120, all lymphocytes, Pandy positive. Weakness of the left arm and leg and the right shoulder girdle

appeared. When discharged on Aug. 9 there was weakness of the shoulder girdle and he walked with a limp. On Aug. 1, 1949 he presented slight weakness of the left leg and the abdominal muscles and walked with a noticeable limp.

Case B. Sister, born Dec. 23, 1940. This child left home to visit her grandmother on June 19, 1948, two days before onset of symptoms in Case A. On June 23 she developed headache and fever, and weakness of one arm appeared the following day. She returned home June 25 with weakness of all four extremities. She was admitted to the N. C. Orthopedic Hosp. June 29 with fever, drowsiness, stiff neck and back, and weakness of all extremities. Response to treatment was slow. She was discharged Aug. 25, 1948 with a right leg brace and bilateral abductor splints. She was followed in clinic, receiving physiotherapy and orthopedic treatment, with gradual improvement noted. She was still under treatment on Aug. 1, 1949, having fairly severe residual involvement of both upper extremities, back and right lower extremity.

FAMILY 19. Twin, white male, born June 16, 1930. On Apr. 13, 1948 he noticed numbness, tingling and weakness of the left arm and leg. On the following day all extremities were weak, he was unable to walk, and fever appeared. On admission to the Central Carolina Convalescent Hosp. on Apr. 15 temperature was 102°F., tendon reflexes were hypoactive bilaterally, and there was difficulty in swallowing and weakness of muscles of the neck, back and all extremities. Spinal fluid: no cells, protein 40 mgms., chlorides and sugar normal. For several days there was no improvement and on Apr. 23 involvement of the left facial nerve was noted. A few days later improvement began and was rapid thereafter. He was discharged May 18 able to walk, but with considerable weakness of all extremities and the neck. One year later there was moderate muscle atrophy in all extremities.

FAMILY 20. *Case A.* Twin, white male, born Sept. 16, 1931. During June, 1935 he began vomiting and had headache and fever. He was treated at home and recovered within two weeks. It was then noted that there was weakness and atrophy of muscles about the right shoulder and right side of the neck. On July 22, 1949 residual weakness and atrophy in this region was still apparent.

Case B. Twin, white male, born Sept. 16, 1941. 4 days after the onset of illness in Case A he also developed fever, headache and vomiting, and the tonsils were enlarged and reddened. 3 days later there was complete paralysis of the left arm and on the following day marked weakness of the right leg. He was treated at home and was unable to sit up for about 5 weeks. He was referred to the N. C. Orthopedic Hosp. Feb. 25, 1936 presenting considerable recovery of function in muscles of the left shoulder girdle, but marked weakness and moderate atrophy of the left biceps and triceps muscles and equinus deformity of the right foot. He was given physiotherapy and muscle reeducation and responded well, being discharged Apr. 24. Operations to correct the foot deformity were done in 1946 and 1947. On July 22, 1949 he still presented moderate atrophy of the left arm and the right calf was 2 in. smaller than the left.

FAMILY 21. Twin, white male, born May 24, 1926. This patient had an acute illness at age 9 months with paralysis of the left arm and leg. A diagnosis of acute poliomyelitis was made at the N. C. Baptist Hosp. and he remained in a spica cast for one year and received orthopedic treatment for 8 years. He did not learn to walk until age 3 years, and then had much atrophy and weakness of the left lower extremity. He was admitted to the N. C. Orthopedic Hosp. from Sept. 27, 1938 to Aug. 23, 1939 presenting atrophy of the left shoulder girdle, extreme scoliosis, and equinovarus deformity of the left foot. A series of opera-

tions and cast procedures corrected the deformities. By Oct., 1939 he could walk well with crutches. In May, 1940 there was one inch shortening of the left lower extremity. He improved gradually with exercise. In Sept., 1949 he presented moderate scoliosis, slight weakness and moderate atrophy of muscles of the left arm and leg, and shortening of the left lower extremity.

FIGURE 2. Dissimilar monozygotic twins (Family 21). The marked difference in appearance is attributed to disturbance in growth in A (on right) secondary to severe paralytic poliomyelitis at an early age.

Dermatoglyphic Formulae:

		Left					*Right*				
		5	4	3	2	1	1	2	3	4	5
Fingers:	Twin A	U	U	U	U	U	W	U	U	W	U
		0–16	0–18	0–20	0–6	0–23	30–20	18–0	19–0	23–11	17–0
	Twin B	U	Tl	W	U	W	W	U	U	W	U
		0–10	7–20	18–19	0–11	15–25	30–14	20–0	18–0	21–14	18–0

Palms:	Twin A	Left	— 7	. 9	. 4	. 3h	. L^R/A^C	. O	. L	. L	. L	.
		Right	— 7	. 5″	. 5′	. 3	. L^R/L^R	. O	. O	. O	. L	.
	Twin B	Left	— 9	. X	. 5″	. 3h	. L^R/A^C	. O	. O	. O	. O	.
		Right	— 7	. 5″	. 9/5″	. 3	. A^R/L^R	. O	. L	. L	. L	.

Key: U = ulnar loop, W = whorl, Tl = "twin loop."

FAMILY 22. *Case A.* Twin, white male, born Apr. 20, 1946. On Feb. 18, 1949 he developed irritability and fever, and was unable to walk on the following day. He was admitted to

Watts Hosp. on Feb. 23 presenting stiffness of the neck and severe weakness of both lower extremities; left otitis media was also present. Spinal fluid: cell count 36, 95% lymphocytes. Chest x-ray showed bronchopneumonia. He responded well to hot packs and a posterior plaster shell. When discharged Apr. 19 there was much weakness of both lower extremities. There was weakness of the legs and a right foot-drop gait in Aug., 1939.

Case B. Brother, born Sept. 13, 1947. One week after onset in Case A, he seemed to have a cold with fever and lost the use of both legs. He was also admitted to Watts Hosp. where a diagnosis of acute poliomyelitis with flaccid paraplegia was made. He remained under treatment for 5 weeks, and had moderate residual weakness of the right leg on discharge. In Aug., 1949 he still walked with a right foot-drop gait.

FAMILY 23. *Case A.* Twin, white male, born Nov. 18, 1946. On July 29, 1948 he developed stiffness of the neck and fever. Because of difficulty in swallowing he was taken to Watauga Hosp., Boone, N. C. where spinal fluid examination showed 350 cells and Pandy positive. He was referred to the Biltmore Orthopedic Home on Aug. 1 presenting dehydration, a stiff neck, quadriplegia, and weakness of the intercostal muscles. The temperature was 103°F. and respiratory difficulty increased. He was placed in a respirator and given fluids with some improvement. On Aug. 6 he suddenly became cyanotic and mucous plugs were aspirated from the larynx. Bronchoscopy was done on Aug. 7 and the right vocal cord was paralyzed at that time. Fever was sustained at a high level, and the child expired on Aug. 8, 1948. Final diagnosis was acute bulbar poliomyelitis.

Case B. Twin, white male, born Nov. 18, 1946. Three days after onset of poliomyelitis in his twin, this child developed symptoms of a cold and had fever. Symptoms subsided in two or three days with no evidence of paralysis at any time.

FAMILY 24. Twin, white male, born June 17, 1926. On Sept. 6, 1941 he developed sore throat and fever followed by vomiting. One week later he developed stiffness and pain in the back of the neck and in the right leg. The right leg became paralyzed on the following day. The family physician made a diagnosis of acute poliomyelitis and he was treated at home, with recovery from acute symptoms. Weakness of the right leg persisted for about one year under treatment, and he walked with a marked limp. On July 22, 1949 there was minimal residual weakness of the right leg and a limp that appears only after exertion.

FAMILY 25. *Case A.* Twin, born Dec. 2, 1937. On Aug. 4, 1948 while on vacation at a beach in South Carolina, he developed vomiting and fever. On Aug. 6 he was unable to swallow. He was taken to a hospital in Conway, S. C. where spinal fluid examination is said to have shown a cell count of 150. By this time he was having difficulty in breathing. He was transferred to the Charlotte Memorial Hosp. by ambulance, but became rapidly worse en route, being unable to breathe and requiring artificial respiration. He was moribund on arrival at the hospital and expired 15 min. later in spite of artificial respiration, laryngeal suction and intracardiac stimulation. A diagnosis of acute bulbar poliomyelitis was made.

Case B. Twin, white male, born Dec. 2, 1937. On Aug. 8, 1948, two days after the death of his twin, he had fever of 101°F. and seemed drowsy. Spinal fluid examination that night revealed cell count 93, predominantly lymphocytes, and positive Pandy. He was admitted to the N. C. Orthopedic Hosp. on Aug. 9 presenting moderate pharyngitis, slight difficulty in swallowing, stiffness of the neck and spasm of the hamstring muscles bilaterally. On Aug. 10 he was completely unable to swallow. Treatment was vigorous, but he continued to become worse. On Aug. 12 there was evidence of severe involvement of both respiratory and cardiovascular systems, and the patient expired, death being attributed to acute myocarditis due to acute bulbar poliomyelitis.

FAMILY 26. Twin, white male, born 1930. For about one week during Aug., 1948 he complained of mild intermittent headache. On Aug. 12 headache became more severe and was associated with nausea, vomiting, fever and pain in the back of the neck. He was taken to St. Leo's Hosp., Greensboro, N. C. where a diagnosis of poliomyelitis was made, and referred to the Central Carolina Convalescent Hosp., being admitted on Aug. 13. He presented stiffness of the neck and spasm of the back and hamstring muscles. Temperature was 102.6°F. Spinal fluid: cell count 60, protein 60 mgms. He was treated with hot packs, hot tubs, and muscle stretching, with prompt response. He was discharged on Aug. 27, 1948 with no residual paralysis. No residua were found on May 25, 1949.

FAMILY 27. Twin, white female, born May 31, 1947. On Aug. 15, 1948 she developed fever and sore throat. Two days later she was unable to sit up and had flaccid paralysis of the right leg. She was admitted to Duke University Hosp. where a diagnosis of acute poliomyelitis was made. She responded rapidly to hot packs and physiotherapy and was discharged two weeks later with only moderate weakness of the right leg. One year later there was still moderate weakness and slight atrophy of the right leg.

FAMILY 28. Twin, white male, born Aug. 23, 1926. On Sept. 27, 1929 he awakened with fever and vomiting. On the following day he was unable to stand alone. The family physician made a diagnosis of poliomyelitis with paralysis of the left leg on Sept. 29, and the patient was treated at home. On recovery from the acute phase there was severe atrophy of muscles of the entire left lower extremity, and he was unable to walk. He was referred to an orthopedic surgeon and fitted with a brace and taught to walk with crutches. An operation to correct deformity was done in 1935. Since then he has been able to walk with a full leg brace with built-up shoe and cane, and has been followed in an orthopedic clinic. In 1949 he presented severe atrophy of muscles of the entire left lower extremity with shortening of nearly three inches.

FAMILY 29. *Case A.* Twin, white female, born Jan. 18, 1943. She developed pain in the back of the neck, headache and fever on Aug. 8, 1948. Pharyngitis was noted and fever persisted in spite of sulfonamides and penicillin. She was referred to the N. C. Baptist Hosp. Aug. 12 presenting marked rigidity of the neck and spasm of the back muscles. Spinal fluid: cell count 129, 10% polymorphonuclears, 90% mononuclears; sugar 70 mgms.; Pandy negative. She responded promptly and was discharged Aug. 22. No residua were noted in July, 1949.

Case B. Brother, born Feb. 1, 1941. Shortly after Case A was admitted to the hospital, this child had fever and complained of pain in the left leg for several days. This cleared spontaneously and he had no further symptoms.

Case C. Sister, born July 20, 1945. This child also had fever as high as 105°F. at the same time as Case B. No paralysis was noted and she recovered spontaneously in about 5 days.

FAMILY 30. Twin, white female, born Jan. 14, 1946. On Sept. 26, 1947 she developed fever and remained listless for 3 days. The physician then discovered paralysis of both legs, and she was referred to the N. C. Orthopedic Hosp. on Oct. 1. There was stiffness of the neck and back, weakness of the left arm and paralysis of both lower extremities with absent reflexes. Spinal fluid: cell count 16, all lymphocytes, Pandy positive. The use of a respirator was required from Oct. 2 to Oct. 15. Orthopedic treatment was begun on recovery from the acute phase, and by Mar. 28, 1948 she was able to walk with a right leg brace. She was discharged on Apr. 18 and treatment continued in the clinic. On July 5, 1949 there was severe

atrophy of the right lower extremity, mild atrophy of the left deltoid, and a leg brace was required for walking.

FAMILY 31. *Case A.* Twin, white female, born Sept. 2, 1939. This child became ill with fever, severe headache and pain in the neck about June 25, 1944. She became unable to walk 3 days later and was admitted to the N. C. Orthopedic Hosp. on July 2. There was generalized muscular tenderness, spasm of muscles along the spine and paralysis of practically all muscles of the left lower extremity. She presented whooping cough on admission and contracted measles while in the hospital. She responded fairly well to treatment and was discharged Dec. 5, 1944 with a single leg brace to the left lower extremity. She was followed in the clinic at regular intervals showing marked atrophy of the left lower extremity, findings being static for several years. A foot stabilization operation was recommended in June, 1949.

Case B. Sister, born Mar. 14, 1937. About 5 days before onset of symptoms in Case A, this child developed fever and headache. About one week later stiffness of the neck and weakness of the legs appeared. She was admitted to the N. C. Orthopedic Hosp. on July 2, 1944 presenting stiff neck and back and partial paralysis of both lower extremities. She responded well and presented only minimal atrophy of the left thigh when discharged on Dec. 5, 1944. In June, 1949 there was slight weakness of the left thigh but no demonstrable atrophy.

Case C. Sister, born July 16, 1944. On Aug. 5, 1948 she developed headache and fever. On Aug. 7 paralysis of the left leg appeared and she was admitted to the N. C. Baptist Hosp. on Aug. 8. She presented fever of 101.8°F., marked rigidity of the neck and back, flaccid paralysis of the left lower extremity, and bladder paralysis with distention reaching the umbilicus. Spinal fluid: cell count 139, 98% monocytes; Pandy positive, culture sterile. The acute phase responded well and she was transferred to a convalescent center on Aug. 19, still presenting paralysis of left lower extremity and weakness of the right. She remained at the convalescent center for 10 months and was discharged with a left leg brace.

FAMILY 32. *Case A.* Twin, white male, born June 24, 1937. During June, 1948 he was lethargic and anorexic for 2 or 3 days, then developed high fever. 2 days after onset of fever he became unable to talk, and the neck was painful and stiff. He was referred to Rex Hosp. on June 19 presenting pharyngitis, left facial paralysis, stiff neck and spasm of the back and hamstring muscles. Spinal fluid: cell count 89, Pandy positive, protein 45 mgms. He was unable to speak, but was able to swallow. He responded well, fever abating by June 21, and regained some ability to speak by June 23. When discharged on July 9 he presented no residual signs. No residua were apparent in Sept., 1949.

Case B. Twin, white male, born June 24, 1937. A few days after onset of poliomyelitis in his twin, he became ill with symptoms resembling a cold. He was admitted to the Moore County Hosp. for 5 days, recovering spontaneously with no paralysis noted. He was discharged with a diagnosis of "abortive poliomyelitis," and was in good health in Sept., 1949.

FAMILY 33. Twin, white male, born Dec. 22, 1942. On Aug. 15, 1948 he developed fever and sore throat, and was thought to have tonsillitis. On Aug. 17 he was unable to stand alone, and was admitted to the N. C. Orthopedic Hosp. Aug. 18 presenting stiffness of the neck and back, complete flaccid paralysis of the left lower extremity, and severe weakness of the right hip flexors and quadriceps. Spinal fluid reported as "cells increased" and Pandy positive. He improved rapidly and on Sept. 6 was transferred to the Charlotte Memorial Hosp., and received physiotherapy there for 4 months. On discharge he was able to walk

with a left leg brace. On Aug. 11, 1949 he presented weakness and moderate atrophy of the left lower extremity and required a brace for walking.

FAMILY 34. *Case A.* Twin, white male, born May 15, 1941. On Sept. 29, 1948 he developed a "cold" with headache and fever lasting 2 days. On Oct. 2 he again had fever, with severe headache and pain in the legs. Paralysis of the legs was noted Oct. 6, and he was admitted to the Central Carolina Convalescent Hosp. on Oct. 8. He then presented paralysis of all extremities, the intercostal muscles, and the right side of the diaphragm, and there was difficulty in swallowing. A tracheotomy was done. He was critically ill for nearly a month, and began to show improvement about Nov. 20. Response to physiotherapy, muscle reeducation and orthopedic treatment was slow but definite. He was discharged on Aug. 31, 1949 able to walk with crutches and a right leg brace, but showing fairly severe residual involvement of all extremities.

Case B. Twin, born May 15, 1941. At the onset of illness in his twin, this child also had a "cold" with headache and fever. He recovered spontaneously in about 3 days and had no further symptoms.

Case C. Brother. born Mar. 30, 1936. He also developed a "cold" with sore throat, headache and fever at the same time as the twins. He recovered spontaneously in about 3 days and had no further symptoms.

FAMILY 35. *Case A.* Twin, white male, born Nov. 3, 1947. During the latter part of Aug., 1948 he suddenly developed fever and symptoms of a cold. 2 days later paralysis of the left leg appeared. On the following day a spinal tap by the family physician was reported as "positive for poliomyelitis" and he was referred to the Central Carolina Convalescent Hosp. On admission he presented a stiff neck and back and flaccid paralysis of the left lower extremity. He responded slowly to treatment and was still in the hospital on May 13, 1949 presenting moderate residual weakness and atrophy of the left lower extremity.

Case B. Sister, born Nov. 23, 1929. At the time of onset of poliomyelitis in Case A, she also developed a "cold" with fever, headache, sore throat and some stiffness of the neck. This subsided spontaneously in a few days and there were no further symptoms.

FAMILY 36. Twin, white female, born Sept. 26, 1941. On Aug. 7, 1948 she developed fever, sore throat, headache, and pain in the neck and back. She was admitted to Grace Hosp., Morganton, N. C. on Aug. 10 presenting marked neck and back rigidity and weakness of muscles of both hips, thighs and legs. Spinal fluid: cell count 110, all lymphocytes, Pandy positive. Involvement of the upper extremities appeared within a few days. She began to improve about Aug. 18 and was transferred to the Emergency Poliomyelitis Hosp., Monroe, N. C. Aug. 25. She received physiotherapy and orthopedic treatment until May 5, 1949 and made good recovery of function in the lower extremities, but still presented marked weakness of the back muscles and the left shoulder was practically flail on discharge. Improvement was noted on examination at the clinic of the N. C. Orthopedic Hosp. on June 7 and Aug. 23, 949. She still required a body support on Oct. 18, 1949.

FAMILY 37: Twin, white male, born Nov. 15, 1938. During the latter part of June, 1943 he developed fever and headache. On the third day he was unable to turn his head and could walk only with extreme difficulty. He was admitted to the Edgecombe General Hosp. and a diagnosis of poliomyelitis was made. He was transferred to Duke University Hosp. July 5, presenting fever of 103°F., stiffness of the neck and back, flaccid paralysis of the left lower extremity, weakness of the right lower extremity and bladder paralysis. Spinal fluid: cell

count 90, Pandy positive. He improved and was transferred to the N. C. Orthopedic Hosp. Aug. 17. He gradually improved under orthopedic treatment and was discharged July 8, 1944 with bilateral leg braces. He was followed in clinic and readmitted to the N. C. Orthopedic Hosp. Feb. 25, 1947. A foot stabilization operation and tendon transplant was done on Mar. 7 and he was discharged improved on May 29. In Aug., 1949 he was able to walk fairly well with a right single leg brace.

FAMILY 38. Twin, white female, born Mar. 31, 1945. On June 27, 1948 she developed a "cold" with fever of 102°F. Severe weakness of the legs appeared July 2. A lumbar puncture done July 3 at the Charlotte Memorial Hosp. showed a cell count of 182 with 82% lymphocytes, proteins 29 mgms. She was transferred to the N. C. Orthopedic Hosp. July 4 presenting complete flaccid paralysis of both lower extremities, no function of the intercostal muscles, generalized weakness of both upper extremities, weakness of the neck and facial hemiparesis. A respirator was required. The acute phase subsided, but severe paralysis remained. She was transferred back to the Charlotte Memorial Hosp. July 30, and with physiotherapy became able to stand with double leg braces. Then for 4 months there was no improvement, so she was transferred to the Warm Springs Foundation Hosp., Warm Springs, Ga. on Feb. 9, 1949. She made gradual improvement and returned home on Nov. 1, 1949. On Sept. 1, 1950 she was able to walk with a left leg brace, but was scheduled to return to Warm Springs for further treatment on Sept. 19.

FAMILY 39. Twin, white male, born Oct. 23, 1933. During the latter part of Feb., 1942 he developed weakness of both legs and fever. 2 days later there was severe weakness of both legs and moderate weakness of one arm, and a diagnosis of poliomyelitis was made, but a lumbar puncture was not done. He was treated at home and one month later presented only slight residual weakness. No residua were present on Aug. 30, 1949.

FAMILY 40. Twin, colored female, born Aug. 38, 1946. On July 27, 1948 she developed fever, malaise, weakness in walking and stiffness of the neck and back. She was admitted to the Asheville Orthopedic Home on July 28 with the above findings plus absent patellar reflexes. Spinal fluid: cell count 56, Pandy positive. Fever continued for a week, then improvement began. There was slight residual weakness of both thighs when discharged Aug. 22. On July 27, 1949 no residual weakness was apparent.

FAMILY 41. Twin, colored male, born June 23, 1944. During July, 1948 he developed pain in the back followed shortly by fever. On the following day the neck was stiff and marked weakness of both legs appeared that night. A lumbar puncture was done by the family physician and was reported to be "positive," but data are not available. He was treated at home and the house was quarantined. He remained in bed for 2 weeks, and then could walk only with great difficulty because of weakness of the right leg. There was apparent shortening of the Achilles tendon and he could not put the right heel to the floor for several months. He improved on exercise and presented only minimal weakness of the right leg on July 31, 1949.

FAMILY 42. Twin, colored female, born Feb. 24, 1947. On Aug. 18, 1948 she developed fever as high as 104°F. and was very irritable. She was admitted to the Central Carolina Convalescent Hosp. Aug. 21 presenting weakness of the flexors of the neck, stiffness of back muscles and weakness of both lower extremities with diminished reflexes. Spinal fluid: cell count 200, Pandy positive. On recovery from the acute phase there was marked weak-

ness of the lower extremities, which slowly improved. She was still in the hospital on May 24, 1949 learning to walk with a leg brace.

FAMILY 43. *Case A.* Twin, colored female, born Nov. 23, 1946. On July 19, 1948 she developed fever and headache. A few days later there was pain in the right leg, followed by difficulty in use of this extremity. She was admitted to St. Agnes Hosp., Raleigh, N. C. on July 26 presenting stiffness of the neck and partial paralysis of the right lower extremity. Spinal fluid: cell count 7 lymphocytes, Pandy negative. Paralysis of the right lower extremity became complete on the following day. Under treatment she recovered except for right foot drop. She was discharged Oct. 1 with a right spring brace. She was followed in the clinic of the Central Carolina Convalescent Hosp., receiving physiotherapy with some improvement. A brace was still required on Oct. 18, 1949.

Case B. Twin, colored female, born Nov. 23, 1946. About one week after onset of poliomyelitis in her twin, this child developed fever, sore throat and severe headache. There was stiffness of the neck and paralysis of the left leg appeared 2 days later. The acute episode subsided within 7 to 10 days, but there was residual weakness of the left leg which responded to physiotherapy. No residua were apparent on Oct. 18, 1949.

FAMILY 44. *Case A.* Twin, white female, born May 6, 1947. This child presented relatively mild congenital cerebral palsy from birth, with moderate spasticity of all four extremities. Fever and laryngitis appeared Aug. 7, 1948. Paralysis of the left leg and unusual stiffness of the neck and back were noted by the family physician on Aug. 10. She was admitted to Grace Hosp. Aug. 12. Spinal fluid: cell count 42, all lymphocytes, Pandy positive. Within a few days there was flaccid paralysis of both upper extremities and the right lower extremity, the left lower extremity remaining spastic. There was some respiratory difficulty, but a respirator was not required. She improved on treatment, and muscle power was regained by Sept. 24 and signs of spasticity reappeared. She was discharged on Oct. 2, but evaluation concerning possible residual effects was difficult because of the cerebral spastic status. On July 14, 1949 she presented obvious evidence of cerebral palsy and could neither walk nor talk.

Case B. Twin, white female, born May 6, 1947. This child had a normal developmental history. She also became ill with fever and laryngitis at about the time paralysis appeared in Case A. She recovered completely within a week with no evidence of paralysis.

FAMILY 45. *Case A.* Twin, white male, born Oct. 20, 1943. On July 19, 1948 he developed fever, severe headache and sore throat. He was admitted to Rex Hosp. July 20, and the spinal fluid is recorded as "positive," but details not available. On July 21 he presented quadriplegia, respiratory paralysis and unconsciousness, and was placed in a respirator. He was semi-comatose for two weeks and paralysis of the vocal cords was noted. He improved rapidly thereafter and was discharged Oct. 17, 1948 with only slight weakness of the lower extremities and the left arm, but almost complete paralysis of the right arm. He continued to receive physiotherapy, with good recovery of function except in the right arm. On July 22, 1949 there was practically no voluntary motion possible at the right shoulder and elbow, and flexion and extension of the right wrist and fingers was quite weak.

Case B. Twin, white male, born Oct. 20, 1943. This child presented congenital spastic paraplegia, with spacticity of both lower extremities. On July 23, 1948 (four days after onset of poliomyelitis in his twin) he also developed fever and pharyngitis. He was admitted to Rex Hosp. on July 24. In addition to the spasticity of the lower extremities previously present, he presented left facial weakness, loss of gag reflex, difficulty in swallowing, stiff

neck and weakness of the upper extremities. Spinal fluid: cell count 202, Pandy positive, culture sterile. The course was stormy and he remained semi-comatose for two days, then improved. He was discharged Aug. 7 and it was felt that there were no residua, although the status regarding spastic paraplegia was unchanged. Condition was unchanged July 22, 1949.

Case C. Brother, born Jan. 4, 1939. On the day following onset of illness in Case B, this child developed fever, nausea, vomiting, headache and stiff neck. He was admitted to Rex Hosp. July 25, 1948 with temperature 103°F., rigidity of the neck and back and spasm of the hamstring muscles. Spinal fluid: cell count 23, Pandy positive, culture sterile. He improved promptly, temperature subsided July 29, and he was discharged without residua on Aug. 7. No residua were found on July 22, 1949.

FAMILY 46. *Case A.* Twin, white male, born Jan. 31, 1946. On July 12, 1948 he developed fever and sore throat. On July 15 weakness of the right arm appeared and he was admitted to the Central Carolina Convalescent Hosp. He presented fever of 102°F., stiff neck and back, and partial paralysis of the right upper extremity. Spinal fluid: cell count 100, 70% lymphocytes; Pandy positive. Paralysis of the entire right upper extremity became complete, and severe weakness of the neck muscles appeared. Recovery was slow; there was still marked weakness and moderate atrophy about the right shoulder when he was discharged Feb. 9, 1949. Findings were essentially unchanged six months later.

Case B. Twin, white male, born Jan. 31, 1946. About one week before onset of poliomyelitis in his twin, this child had fever to 104°F., and sore throat for 3 days. On the day his twin was admitted to the hospital fever, vomiting and headache recurred. Mild symptoms lasted one week, but paralysis was not observed.

DISCUSSION AND CONCLUSIONS

Before analysis of the family data is attempted, it seems advisable to assess the completeness of ascertainment of the twin series. As was mentioned above, of the 3890 reported cases of poliomyelitis that were classified regarding twinning, 56 were found to be of plural birth. This gives a plural birth rate in this series of cases of 1 in 69.46 births, or 1.440 ± 0.191 per cent. One set of triplets is included in the 56 index families, and if this family is eliminated, the twin birth frequency becomes 1 in 70.71 births or 1.414 ± 0.189 per cent. The frequency of twin births in the total United States population has been determined by Strandskov (1945) as 1 in 86.13 births or 1.161 per cent, and the frequency of triplets as 1 in 8,411 births or 0.01189 per cent. The difference between the observed twin birth rate in this series and the rate determined by Strandskov is 0.253 per cent, this difference being 1.33 times its standard error and non-significant. The frequency of twins ascertained in the series of 3890 cases of poliomyelitis does not differ significantly from the corresponding frequency for the total United States population.

The proportions of twins of various types in the observed series should also give information regarding completeness of ascertainment. Strandskov and Edelen (1946) have estimated the percentage of monozygous twins among all twins in the total United States population to be 33.46 per cent, and it is generally accepted that the ratio of like-sexed to unlike-sexed pairs among

dizygous twins is approximately 1:1 as suggested by Weinberg (1902). Again eliminating the one set of triplets from consideration, the observed data include 45 pairs of twins, 14 pairs diagnosed as monozygous and 31 pairs as dizygous. The observed ratio of 14:31 is in good agreement with the expected ratio of 15.06:29.94 ($\chi^2 = 0.12$). Under the assumption of equal proportions of like-sexed and unlike-sexed dizygous pairs, the expected ratio would be 15.5:15.5 and the observed ratio 12:19, the deviation from expectancy again being non-significant ($\chi^2 = 1.58$). It therefore seems reasonable to conclude that ascertainment of twin pairs within the total series of poliomyelitis cases is practically complete, the deviation from expectancy actually being in the direction of an excess of twins, and the proportion of monozygous to dizygous pairs is in agreement with expectancy.

In all 7 cases where both members of a twin pair developed paralytic poliomyelitis both were discovered independently through their individual report cards; the family investigations brought to light no secondary cases amongst the twins themselves. This fact is indicated in table 1 by marking both members of such concordant pairs as *propositi*. This evidence is again consistent with the assumption of complete ascertainment of cases amongst twins. It could be argued, however, that two cases developed within the same family at nearly the same time would be apt to increase the likelihood of each case being reported. If such a preferential recording of concordant pairs has occurred, however, there is at least no internal evidence of the bias having been exercised differently in the two zygosity classes.

A priori, there is no reason to suspect that twins might be significantly more or less susceptible to poliomyelitis than single-born individuals. No evidence is produced by this study which would suggest any general difference in susceptibility status due to twinning *per se*, and the figures cited above might be considered as offering some evidence against such a suggestion. It is therefore assumed for purposes of this analysis that twins in general are neither more nor less susceptible to paralytic poliomyelitis than single-born individuals.

In estimating concordance rates in this material, individuals were considered as "affected" if they presented any demonstrable degree of paralysis during the acute phase of the illness, regardless of whether there was residual paralysis after recovering from the acute phase. Even though his illness may have been diagnosed as "acute non-paralytic poliomyelitis", any individual not having evidence of paralysis was classed as "unaffected." This criterion of division was adopted because of the known gradual and almost imperceptible gradation in severity of cases of proved poliomyelitis from the most severe, with bulbar paralysis, involvement of vital centers in the brain stem and rapid fatal termination (as in family 25) to the mildest "abortive" cases that may only be diagnosed with certainty by virus studies. Although severity of involvement may be clinically assigned to various categories, such as bulbar.

quadriplegic, diplegic, monoplegic, etc., such gradations are at best artificial and transitional cases exist between all grades. As the presence of paralysis in any degree is generally considered evidence of invasion of the central nervous system by the virus, it was felt that this study should be primarily concerned with paralytic cases, and in essence would investigate susceptibility of the central nervous system to viral invasion rather than any type of local respiratory or systemic involvement. Twin pairs were therefore considered as concordant only if both had evidence of muscle paralysis. The concordance table below was constructed on this basis, including data on 45 twin pairs and one set of two-egg triplets. The set of triplets (family 5) consists of an affected male and two non-affected females, the females being derived from a single ovum. This set is classed as two pairs of dizygous discordant twins in the following table:

	Concordant	*Discordant*	*Totals*
Monozygous	5	9	14
Dizygous	2	31	33
Totals	7	40	47

$\chi^2 = 6.81$, D. F. = 1

It is thus demonstrated that both members of monozygous twin pairs present paralytic poliomyelitis more often than do dizygous pairs, and that this difference is statistically significant with a probability level of less than 1 per cent ($P = 0.0091$).

TABLE 2. PERCENTAGE OF PARALYTIC POLIOMYELITIS OCCURRING AMONG COGNATES OF INDEX TWIN CASES

RELATIONSHIP	TOTAL	PARALYTIC POLIOMYELITIS	PERCENTAGE ± STANDARD ERROR
Monozygotic co-twins	14	5	35.71 ± 12.81
Dizygotic co-twins	33	2	6.06 ± 4.15
All sibs	155	7	4.51 ± 1.67
"Exposed" sibs	101	7	6.93 ± 2.53
Half-sibs	4	0	
Parents	87	0	
Uncles-aunts*	516	7	1.36 ± 0.51
Nephews-nieces*	39	1	2.56 ± 2.53
First cousins*	885	4	0.45 ± 0.22

* Information in these categories based on history rather than examination.

The incidence of paralytic poliomyelitis was also estimated for relatives as close or closer than first cousins of the twin index cases. It should be emphasized that information regarding twin partners, sibs and parents was obtained by direct examination of the individuals in question, but that information regarding uncles, aunts, nieces, nephews and first cousins is generally based on

history furnished by the parents of the twins. The same degree of reliability cannot be ascribed to the last three categories in table 2. The sibs are classified in two ways, one estimate being for all sibs, and the estimate for "exposed sibs" being based only on the number of sibs living in the same household with the affected twin at the time of onset of acute poliomyelitis, under such conditions that it may be assumed that exposure to a virulent virus occurred.

Although these data present evidence of the existence of a measurable genetic influence on susceptibility to the paralytic form of poliomyelitis, they do not permit us to reach any conclusions concerning the number or kind of genes conditioning such susceptibility. The fact that no cases of paralysis were encountered among the 87 examined parents leads one to believe that a dominant gene, even with greatly reduced penetrance, would not produce the observed results. Although the sex ratio of affected persons in this series shows a slight excess of males, in a ratio of 38:22 ($\chi^2 = 4.27$), there is no suggestion of the action of sex-linked genes in the family data. Addair and Snyder (1942) have suggested that susceptibility may be conditioned by a recessive gene with about 70 per cent penetrance. No critical evaluation of the suggestion that a recessive gene is involved is made from these data, but the concordance rate in monozygotic twins would suggest that the penetrance might be in the neighborhood of 35 per cent if this theory is correct. Using a penetrance rate of $\frac{5}{14}$ these data are at least compatible with the interpretation of Addair and Snyder, as is indicated by the non-significant differences between the observed incidence of paralysis in sibs of twin index cases and expected values calculated on this basis:

CLASS OF SIBS	PARALYTIC POLYMYELITIS AMONG SIBS		NORMAL SIBS		CHI-SQUARE (D.F. = 1)
	Observed	Expected*	Observed	Expected	
Dizygous co-twins	2	2.946	31	30.054	0.334
All sibs	7	13.839	148	141.161	3.711
"Exposed" sibs	7	9.018	94	91.982	0.496

* Expected frequency $= \frac{5}{14} \cdot \frac{1}{4} \cdot N$, where N = total number of sibs observed.

If the homozygous state of a recessive gene determines genetic susceptibility to paralysis, this gene must have a relatively high frequency in the total population, and heterozygotes must be quite numerous. Although no provisional estimate of gene frequency may be made from these data, the absence of cousin marriages among parents of the affected twins is indicative of a relatively high figure. We were unable to obtain information on this point in two families, but in 44 families we can specify that the parents are not closer kin than third cousins (coefficient of relationship = 0.0078 or less). If a rare reces-

sive gene were involved, a significant proportion of cousin marriages should have been encountered among these parents.

Another possible interpretation of these findings is that susceptibility may be due to multiple gene effects. The data are insufficient for critical evaluation of this possibility.

The observed concordance rate of 35.7 per cent for monozygous twin pairs would seem to indicate that environmental factors are of major importance in determining the reaction to exposure even in persons of identical genetic endowment. The possibility that the susceptibility status may vary from time to time in the same presumably genetically susceptible individual is suggested by the situation in families 11 and 31, where paralytic cases appeared in different children in the sibship in the 1944 and 1948 epidemics, although those being affected in 1948 were also presumably exposed in 1944. Considerable study of environmental factors which may influence the susceptibility status has been done elsewhere, and will not be reviewed here. It is to be hoped that future work in this field may recognize that the susceptibility status apparently has both a genetic and an environmental component, and that simultaneous evaluation of both components should be more productive of results than study of either one alone.

SUMMARY

1. An unselected series of 3890 reported cases of poliomyelitis was searched for twins; 46 families were located containing twins or triplets, one or more having had paralytic poliomyelitis while living with the twin partner.

2. Case histories of all paralytic, non-paralytic and suspected cases of poliomyelitis in the 46 families are presented.

3. Test factors are presented for all available members of the 46 families including ABO blood groups, MN blood types, Rh classification, secretor factor, and PTC taste test. Palmar dermatoglyphics and photographs of the twins were obtained.

4. With regard to the paralytic form of poliomyelitis, twin pair concordance was found in 35.7 per cent of 14 monozygous pairs and 6.06 per cent of dizygous pairs, this difference being statistically significant.

5. We conclude that the existence of a genetic factor controlling, at least in part, susceptibility to the paralytic form of poliomyelitis is demonstrated.

6. No conclusion concerning the genetic mechanism involved may be reached, but the data are at least compatible with the theory that susceptibility may be conditioned by the homozygous state of a recessive gene with approximately 35 per cent penetrance.

7. It is emphasized that the status of susceptibility to paralysis in poliomyelitis apparently has both a genetic and an environmental component, and

both factors should be simultaneously evaluated in studies aimed at prevention of the disease.

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A Genetic Study of Mediterranean Anaemia in Cyprus

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INTRODUCTION

THIS study of Mediterranean anaemia was made during a period of military service in Cyprus. The existence of the disease in Cyprus has only been recognised in recent years. Aravantinos (1936) mentioned that he had seen cases from Cyprus, and two of the children mentioned by Caffey (1937) were of Cypriot parentage. In the island itself, Fawdry (1944) was the first to draw attention to the condition.

An accurate definition of what constitutes the disease has not been given in the literature. There is in fact a gradual gradation from the trait not showing any anaemia, through the mild form of the disease, compatible with adult life, to the severe form of the disease, fatal in infancy. Clearly, any distinction between one form and another is purely arbitrary. The terms Thalassaemia major and minor have been used to differentiate between the severe and mild forms of the disease. Classification is considered in greater detail subsequently.

Fourteen cases of the disease, together with their relatives, were examined. Detailed case histories are not presented, although the haematological data on these cases and their relatives are recorded in table 1. An investigation to determine the incidence of the trait of the disease is recorded. A survey of a mountain village was made to show how the trait can affect one isolated community.

DIFFERENTIATION OF THE TRAIT FROM THE DISEASE

Before discussing the disease and the trait, it is necessary to define what constitutes each of them and how they are differentiated. This is difficult. Wintrobe *et al.* (1940) described mild forms of the disease compatible with adult life, referring to them as thalassaemia minor to contrast them with thalassaemia major, the severe form found in infancy. He did not state, however, any clear-cut differentiation, and some of his mild cases were what are now referred to as the trait. Smith (1943) discussed the diagnosis of the trait, but he did not clarify the differentiation. For the purpose of discussion I shall refer to the trait when there is no anaemia or only mild anaemia and no circulating normoblasts, and to the disease when the anaemia is more severe and circulating normoblasts are seen. This distinction is a purely arbitrary one,

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TABLE 1. SUMMARY OF HAEMATOLOGICAL DATA AND OTHER TRAITS STUDIES IN TEN CYPRIOT FAMILIES

Column headings in this table are as follows: PED. No., subject identified by pedigree generation and position numbers as shown in figure 1, SEX; HB, hemoglobin, grams per cent; RBC, erythrocyte count, in millions per cubic mm.; RET, reticulocytes, per cent total erythrocytes; NUC, nucleated erythrocytes, per 100 leucocytes; A-P, anisocytosis and/or poikilocytosis; TAR, "target cells"; OVC, ovalocytes; MIC, microcytes; FRAG, fragility in NaCl, grams per cent.; BT, blood types ABO and Rh (R = Rh-positive); EC, eye colour (Brn, brown; Haz, hazel; Blu, blue); MEDIT. ANAEM., diagnosis of Mediterranean anaemia, 'trait', or normal condition.

PED. No.	SEX	HB	RBC	RET	NUC	A-P	TAR	OVC	MIC	FRAG	BT	EC	MEDIT. ANAEM.
Family No. 1													
Prop.	♂	5.8	2.59	6	61	+++	+	+	+	.42/.15	A		Dis.
I-1	♂	13.3	3.81	1	0	−	−	−	−	.42/.30	O		Norm.
I-2	♀	12.6	4.99	½	0	+	+	++	+	.42/.24	A		Trait
II-1	♂	15.8	4.69	½	0	−	−	−	−	.45/.30	A		Norm.
II-2	♀	15.1	4.61	1	0	+	+	++	+	.42/.21	A		Trait
II-3	♀	10.0	4.41	1½	0	+	−	+	+	.39/.18	B		Trait
II-5	♀	11.9	4.51	½	0	−	−	−	−	.42/.27	A		Norm.
III-3	♂	15.8	4.89	½	0	+	+	−	−	.42/.27	A		Trait
III-4	♀	13.7	4.61	½	0	−	−	−	−	.45/.30	A		Norm.
III-5	♂	13.4	5.02	1	0	+	+++	+	+	.36/.21	O		Trait
III-6	♀	14.7	4.95	3	0	+	+++	+	+	.42/.21	A		Trait
III-7	♀	12.3	4.66	1	0	+	+	+	+	.39/.21	A		Trait
III-8	♂	14.0	4.80	½	0	−	−	−	−	.42/.30	O		Norm.
III-9	♀	13.0	3.98	½	0	−	−	−	−	.45/.33	A		Norm.
Family No. 2													
Prop.	♀	9.2	3.59	15	9	++	+++	+	+	.45/.15	AB	Brn	Dis.
I-2	♀	14.1	4.67	1	0	−	−	−	−	.42/.27	B	Blu	Norm.
I-3	♂	12.4	4.34	1	0	+	+	+	−	.39/.21	A	Haz	Trait
I-4	♀	12.0	4.33	1	0	+	+	+	−	.45/.18	B	Brn	Trait
II-2	♂	14.8	4.90	1	0	−	−	−	−	.36/.27	B	Brn	Norm.
II-3	♀	13.4	4.10	½	0	−	−	−	−	.39/.30	B	Brn	Norm.
II-4	♂	13.4	4.90	2	0	+	+	+	−	.36/.24	B	Brn	Trait
II-5	♀	11.3	4.20	1	0	+	+	+	−	.39/.24	B	Brn	Trait
II-6	♂	12.3	4.64	2	0	+	+	+	−	.39/.18	AB	Brn	Trait
II-7	♀	12.0	3.98	5	0	+	++	++	−	.39/.18	B	Brn	Trait
II-8	♂	12.7	4.57	1	0	+	−	+	−	.42/.27	A	Haz	Trait
II-9	♀	13.4	5.03	4½	0	+	++	+	−	.39/.18	A	Brn	Trait
II-10	♂	12.3	4.67	1	0	+	++	+	−	.42/.21	A	Brn	Trait
II-11	♀	12.0	4.65	1	0	+	+	+	−	.42/.21	B	Brn	Trait
II-12	♀	14.8	5.70	1	0	+	−	+	+	.42/.27	A	Brn	Trait
Family No. 3													
Prop.	♀	4.9	2.80	10	4	++	+++	++	++	.48/.12	A	Brn	Dis.
I-1	♂	13.4	4.40	1	0	+	+	+	+	.45/.21	A	Haz	Trait
I-2	♀	12.6	4.40	2	0	+	+	−	−	.45/.24	A	Brn	Trait
II-5	♀	12.7	5.60	3	0	+	+	+	−	.45/.21	A	Brn	Trait
Family No. 4													
Prop.	♂	2.8	1.52	28	125	+++	++	++	++	.39/.12	B	Haz	Dis.
I-3	♂	12.7	4.20	½	0	+	++	+	+	.39/.24	O	Brn	Trait
II-3	♂	14.1	5.98	1	0	+	++	+	+	.33/.18	B	Brn	Trait
II-4	♀	14.8	4.20	½	0	+	+	+	+	.42/.12	O	Brn	Trait
II-5	♂	13.4	4.95	1	0	+	++	+	+	.39/.24	O	Haz	Trait
II-6	♀	13.4	4.25	1	0	+	+	+	+	.39/.24	O	Haz	Trait
III-3	♀	3.8	2.20	14	262	+++	+	++	++	.42/.12	O	Blu	Dis.

TABLE 1—*Continued*

PED. NO.	SEX	HB	RBC	RET	NUC	A-P	TAR	OVC	MIC	FRAG	BT	EC	MEDIT. ANAEM.
Family No. 5													
Prop.	♂	9.5	4.20	9	2	+++	++	+	+	.51/.18	OR	Brn	Dis.
I-1	♂	14.0	4.67	3	0	+	+	+	+	.45/.27	AR	Brn	Trait
I-2	♀	13.5	4.33	1	0	+	+	+	+	.45/.24	OR	Brn	Trait
II-1	♀	13.3	4.25	½	0	−	−	−	−	.45/.33	A	Brn	Norm.
II-3	♂	8.5	4.15	11	4	+++	+	+	+	.45/.15	OR	Brn	Dis.
II-4	♀	14.0	4.45	1	0	−	−	−	−	.45/.30	OR	Brn	Norm.
II-5	♀	12.7	4.37	1	0	+	+	+	+	.45/.24	AR	Brn	Trait
II-6	♂	12.1	5.10	3	0	+	+	+	+	.48/.27	OR	Brn	Trait
II-7	♂	4.5	2.80	8	2	+++	++	++	+	.48/.24	AR	Brn	Dis.
II-8	♀	12.7	4.20	½	0	−	−	−	−	.45/.30	OR	Brn	Norm.
III-1	♀	12.2	3.79	3	0	+	+	+	+	.45/.27	O	Brn	Trait
III-2	♀	11.1	4.60	1	0	+	+	+	+	.45/.24	A	Brn	Trait
Family No. 6													
Prop.	♂	4.5	1.83	15	20	+++	++	+	+	.45/.21	O	Brn	Dis.
I-1	♀	12.1	4.55	½	0	−	−	−	−	.48/.27	O	Brn	Norm.
I-2	♂	11.4	4.30	2	0	+	−	+	+	.45/.24	O	Haz	Trait
I-3	♀	10.8	4.36	2	0	+	+	−	+	.42/.21	A	Brn	Trait
I-4	♂	12.7	5.40	½	0	−	−	−	−	.48/.27	A	Haz	Norm.
II-1	♀	10.8	4.52	½	0	−	−	−	−	.48/.33	A	Brn	Norm.
II-3	♀	12.1	4.90	2	0	−	−	−	−	.48/.33	A	Brn	Norm.
II-4	♂	11.4	4.78	2	0	+	+	+	+	.45/.21	O	Haz	Trait
II-7	♂	10.8	4.20	3	0	+	−	+	+	.45/.27	O	Brn	Trait
II-8	♂	10.2	4.56	2	0	+	+	+	+	.45/.24	O	Brn	Trait
Family No. 7													
Prop.	♂	12.0	4.55	29	488	++	++	++	++	.48/.09	O	Brn	Dis.
I-1	♂	15.5	5.65	2	0	+	+	+	+	.42/.21	O	Haz	Trait
I-2	♀	13.4	4.77	1	0	+	+	+	−	.42/.24	A	Haz	Trait
II-1	♀	12.7	4.35	1	0	−	−	−	−	.45/.33	A	Brn	Norm.
II-3	♀	13.4	4.65	1	0	+	−	++	+	.42/.24	A	Brn	Trait
II-4	♂	13.2	4.80	1	0	+	−	+	+	.42/.27	O	Brn	Trait
Family No. 8													
Prop.	♂	6.6	2.55	10	18	+++	+	+	+	.39/.18	A	Brn	Dis.
I-2	♀	12.0	4.10	½	0	+	+	+	+	.36/.21	A	Brn	Trait
I-4	♀	10.6	3.90	1	0	+	+	+	+	.39/.24	O	Brn	Trait
II-3	♂	12.7	4.65	1	0	+	+	+	+	.39/.21	A	Brn	Trait
II-4	♀	11.3	4.35	2	0	+	++	+	+	.36/.21	O	Haz	Trait
II-5	♀	10.6	3.60	1	0	+	+	+	+	.39/.24	A	Haz	Trait
II-6	♀	10.6	4.45	2½	0	+	++	+	+	.36/.21	A	Brn	Trait
III-2	♀	6.5	3.20		7	+++	+	++	++	.36/.18	O	Brn	Dis.
Family No. 9													
Prop.	♀	3.2	1.92	24	167	+++	+	+	++	.42/.21	AR	Brn	Dis.
I-1	♂	13.4	4.11	3	0	+	+	+	+	.42/.27	A	Haz	Trait
I-2	♀	14.8	5.50	1	0	+	+	+	+	.42/.27	O	Brn	Trait
II-1	♂	13.4	4.50	1	0	+	++	+	+	.42/.24	A	Brn	Trait
II-2	♀	12.7	4.70	2	0	+	+	+	+	.45/.24	A	Brn	Trait
III-2	♀	12.7	4.35	1	0	+	+	+	+	.48/.27	A	Brn	Trait
III-3	♂	12.0	3.77	1	0	+	+	+	−	.39/.24	A	Brn	Trait
III-6	♂	11.3	3.80	1	0	+	−	+	+	.45/.24	A	Brn	Trait
Family No. 10													
Prop.	♂	13.1	5.70		+	++	++			.40/.15		Haz	Dis.
I-1	♂	14.0	4.86	½	0	+	+	+	+	.45/.27		Haz	Trait
I-2	♀	14.8	4.86	½	0	+	+	+	+	.45/.27		Brn	Trait
II-3	♂	14.6	5.30	½	0	+	+	+	+	.43/.24		Brn	Trait

since one is dealing with a gradation and not with two distinct entities. Nor is it entirely satisfactory, since under conditions of stress, such as an infection, cases of the trait may become more anaemic and circulating normoblasts may appear. Wintrobe *et al.* (1940) showed that an injection of adrenaline caused the appearance of normoblasts in the peripheral blood in severe cases of the trait. Pietroni (1946) told me of a case with the haematological features of the trait of the disease, who while suffering from rheumatic fever, became anaemic and exhibited circulating normoblasts in the peripheral blood.

TEN FAMILIES

The classical features of the disease have been described on numerous occasions and only the more interesting points relating to genetics brought out by this study will be described.

Until 1940 only the severe form of the disease had been recognised. Wintrobe *et al.* (1940) then described cases of a relatively mild anaemia occurring in adolescents and adults in several Italian families. These cases resembled Mediterranean anaemia as it was then recognised, but they were much less severe. Their observations have been repeatedly confirmed, and the occurrence of this mild form in Cyprus was reported by Fawdry (1946), who recorded six cases. My impression is that every grade from the mildest to the severest occurs, and this is borne out by the series of ten families here described (fig. 1).

The severity of the disease appears to follow a definite familial pattern in the families recorded (table 1). Thus, in family no. 4, the sister of the propositus (S. K.) became severely anaemic like her brother. Their haemoglobin levels were 2.8 and 3.8 gm.%, respectively. In family no. 8 a similar state of affairs was noted. Two cases there had haemoglobin levels of 6.6 and 6.5 gm. % respectively. In family no. 5, two cases had haemoglobin levels of 9.5 and 8.5 gm. % respectively, but the third case did not follow this pattern and had a haemoglobin of 4.5 gm. %. In family 9, the patient had a haemoglobin of 3.2 gm. %, and a brother had died previously of the condition at the age of two years; presumably this had also been a severe case. It will be noted that both the fifth and the seventh families are large. Both show only mild cases of the disease, with the exception of 1 case, and both families have members showing no evidence of the trait—two daughters in each family. It appears, therefore, that there is a tendency to follow a definite familial pattern. Where there are children with this disease in a family, any further affected children will tend to manifest the disease with roughly the same severity. While the series recorded here is obviously too small to be significant, the tendency is clear enough to warrant further investigation. In a paper by Smith (1943) on familial blood studies in cases of Mediterranean anaemia, three of his families have two cases of the disease in each of them. These cases add further support to this hypothesis.

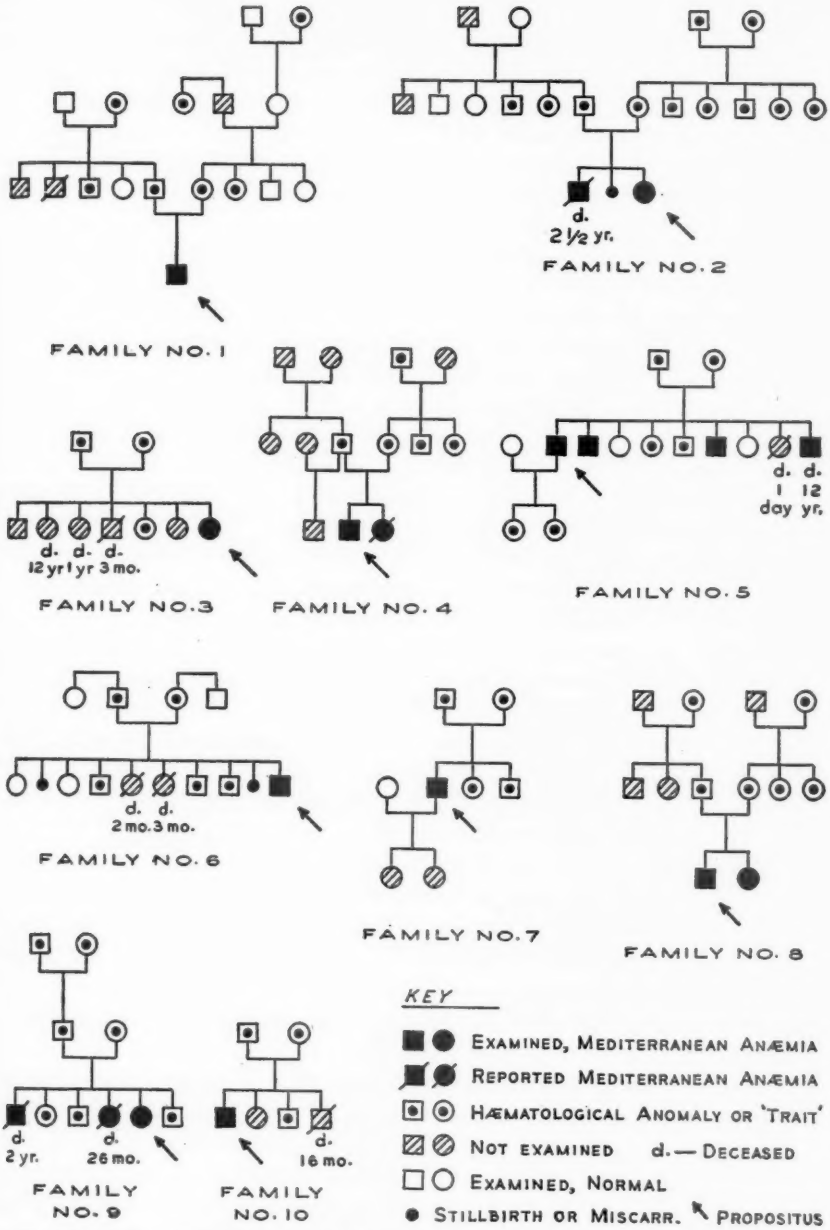

FIG. 1. Pedigrees of ten Cypriot families selected for the presence of Mediterranean anaemia and showing the transmission of the erythrocyte anomaly or trait.

No conclusions could be reached regarding the severity of the disease in the offspring compared with the severity of the trait in the parents. It appeared that there was no definite relationship. Severe cases might result when the parents had a severe degree of the trait, as in the fourth family, and mild cases from parents with a mild degree of the trait, as in the tenth family. A consideration of the other families in this series was so inconclusive, however, that no conclusions could be drawn.

The blood changes, while severe in the case of the disease, may only be slight in the case of the trait. Difficulty was encountered in a number of cases in deciding from the blood film whether or not the trait was present. The problem was sometimes solved by the recognition of target cells, but the difficulty could be very real when these were absent. Smith (1946) stated that members of the family of a case of Mediterranean anaemia should not be regarded as haematologically normal until many slides had been examined. This practice was observed. Fortunately, as the erythrocyte fragility was abnormal in all cases of the disease and the trait, there was a check of the interpretation of the blood film, and error was avoided.

The part played by the Rhesus factor in Mediterranean anaemia was studied to a limited extent. In family no. 5, both parents with the trait were found to be Rhesus positive, as were three cases with the disease. One brother and two sisters with the trait were Rhesus positive, and one sister without the disease or trait was also Rhesus positive. In the ninth family both the patient and her mother were Rhesus positive. From these few observations it appears that the Rhesus factor plays no part in the causation of Mediterranean anaemia. From the behaviour of the disease one would not expect any relationship to the Rhesus factor, since there is no clinical similarity to haemolytic disease of the newborn. In that condition the first child is seldom affected, but there is an increasing incidence and severity in subsequent offspring. Further, if the first month is survived the infant is normal haematologically. By way of contrast, rank in the family bears no relation to the development of Mediterranean anaemia. This was stated by McIntosh and Wood (1942) and it is well borne out by the present study. Further, the condition develops at least months after birth, at a time when the effect of any Rhesus incompatibility should have disappeared.

The series shows that there is no relationship between the disease and the ABO blood groups. Caminopetros (1938) stated that the diseased child always belonged to the same blood group as the carrier parent. His article was written before the trait of the disease was fully understood, and since it has been shown that in almost every case both parents have the trait, his observation is invalidated and there is no evidence of linkage.

Colour of eyes was noted in the families, but no relationship was observed between this inheritance and that of the disease.

INCIDENCE OF THE TRAIT

In view of the frequency of the trait in the families with cases of the disease, it was obviously necessary to determine the incidence of the trait in the general Cypriot population. From the description of the trait already given, it will be clear that the essential features are: (1) the diminished fragility of the erythrocytes in saline, 0.30% saline being the critical value for complete haemolysis; (2) the changes in the blood film, showing anisocytosis and poikilocytosis, with target cells usually present, and often ovalocytes and microcytes.

Determination of the fragility and examination of the blood film was therefore made on 100 Cypriots. These were chosen at random. A large number of them were healthy soldiers, and thus males predominate in the analysis. Soldiers detained on the surgical service of the military hospital were among those examined, but care was taken not to include those suffering from any general disease. The cases were those awaiting procedures such as hernia repairs. The results of the survey may be analysed as follows:

	GREEK	TURK	ARMENIAN	MALE	FEMALE	TOTAL
Normal	56	16	0	70	2	72
Trait	22	5	1	27	1	28
Totals	78	21	1	97	3	100

These figures show an incidence of the trait of 28% in the 100 persons examined. Both Greek and Turkish communities are affected. Clearly the number of people examined is too small to be highly reliable, but it does give an indication of the high incidence of the trait.

It will be noted that it was stated at the beginning of this section that 0.30% saline was taken as the critical point for complete haemolysis. In the cases examined, a few cases, in which haemolysis was not complete until 0.27% saline, have been passed as normal. Such cases always present difficulty, and careful examination of the blood film is necessary before coming to a decision. The problem is all the more difficult, since morphological cell changes in such cases are also minimal.

It became apparent early in this investigation that a high proportion of the general population in Cyprus showed the trait. I pointed this out to Dr. Fawdry, and he had the opportunity to do a similar investigation while conducting a malaria survey. He adopted the same technique, as described subsequently under the village survey, for checking the fragility in 0.30% saline,

but he did not check the blood films. The survey was carried out on Limassol school children with the following results:

	TOTAL	TRAIT	NORMAL	TRAIT PERCENTAGE
Greek Males	224	41	183	18
Females	193	30	163	15
Total	417	71	346	17
Turk Males	62	10	52	16
Females	53	14	39	27
Total	115	24	91	21
Grand Total	532	95	437	18

The figures for Turks are not large enough to make the apparent discrepancy between male and female incidence significant, and probably, as amongst the Greeks, the trait is of equal incidence in the two sexes. This approximately even distribution of the trait between males and females is in contrast to the observation of Fawdry (1947) that the fully developed disease occurs predominantly in males. He had observed more than 100 cases during a period of seven years, and had noted that male children were affected more often than female children in the ratio of 3 to 1.

Neel and Valentine (1945) investigated the incidence of the trait in individuals of southern Italian and Sicilian descent in Rochester, N. Y., between 1928 and 1942. They found 11 cases of the disease, giving one case per 2,368 births. On the assumption that the disease is due to homozygosity for the inherited factor, and the trait due to heterozygosity, this would give an incidence of one per 25 individuals. This agrees well with the actual frequency of the trait found by Silvestroni and Bianco (1949) in Sicily. The latter workers found a frequency varying in various parts of Italy from a fraction of 1% to approximately 10% in certain areas around the Po Valley. Dameshek (1943) found changes in the blood film (target cells or ovalocytes) in 8 out of 60 (13%) unselected Italians in Boston. In none of these surveys has the incidence approached that which has been found in Cyprus.

From the investigations carried out by Dr. Fawdry and myself, it is clear that the trait of Mediterranean anaemia is present in about 20% of the Cypriot population—roughly equally distributed between Greek Cypriots and Turkish Cypriots and between males and females.

A VILLAGE SURVEY

When the results of the analysis of the general populace became apparent, it was an obvious step to find out how the trait and disease manifested them-

selves in an actual village. It was decided to carry out a survey of a whole village.

The village of Alithinou was chosen. This is a village in the Troodos range of mountains, about 3,500 feet above sea level. Villages of this type are very isolated. Each one of them owns a bus, which keeps them in communication with civilisation. For the most part, however, the villagers stay at home looking after their farms. Their families have lived in the same village for generations, and so inbreeding has resulted. As it was very aptly put to me by one of the inhabitants of Alithinou, "The boys cannot now marry the girls because they are related to them." From the point of view of studying the hereditary nature of this disease, however, this was a great advantage.

Alithinou was chosen for the survey for several reasons. The fifth family which was examined in the series came from Alithinou. This therefore meant that the disease and trait were present in the village. This family had been very co-operative and were willing to help. The father of the family (I. N.) was the village Mukhtar—the village chief. Through his co-operation it was possible to examine 65 out of the 80 inhabitants. All were Greek Cypriots.

The technique of the investigation was as follows: 500 cc. of 0.30% saline was prepared, and 20 cc. of 1.6% sodium citrate was added to this solution. The citrate solution was isotonic with the saline. Control experiments with normal individuals and those already known to have the trait showed that it did not affect the fragility end points. The citrate was added to prevent any coagulation when the blood was added to the solution. In previous experiments this had been found occasionally to vitiate results. One cc. of the solution was added to a small agglutination tube, and a drop of blood was added to this from a finger prick. At the same time, two thin blood films were made and subsequently stained.

The survey was made on February 18, 1947. The villagers were most helpful, though they did not understand the significance of the investigation. Certain villagers were not available, either on account of work, or through absence from the village. Fortunately it rained on the day of the survey, and most of the farmers had not gone out to the fields.

The results of the survey are shown graphically in figure 2 to illustrate the families' inter-relationship and the incidence of the trait and the disease. The results may be analysed as follows:

	MALES	FEMALES	TOTAL
Normal	9	25	34
Trait	13	15	28
Disease	3	—	3
Total	25	40	65

It will be seen that about 50% of the people examined showed either the trait or the disease. This unusually high frequency is evidently attributable to the fact that this small village was selected for study because it was known to contain 3 cases of Mediterranean anaemia in family 5 referred to above. It was therefore certain, on the genetic hypothesis, that both parents of these 3 cases should possess the genetic factor. Discounting these parents as well as several other paternal relatives who almost certainly share the *same* factor found in the father, the frequency of the trait among the remaining inhabitants is seen to be about 25%, which is about the same as that found in the general surveys of the island population.

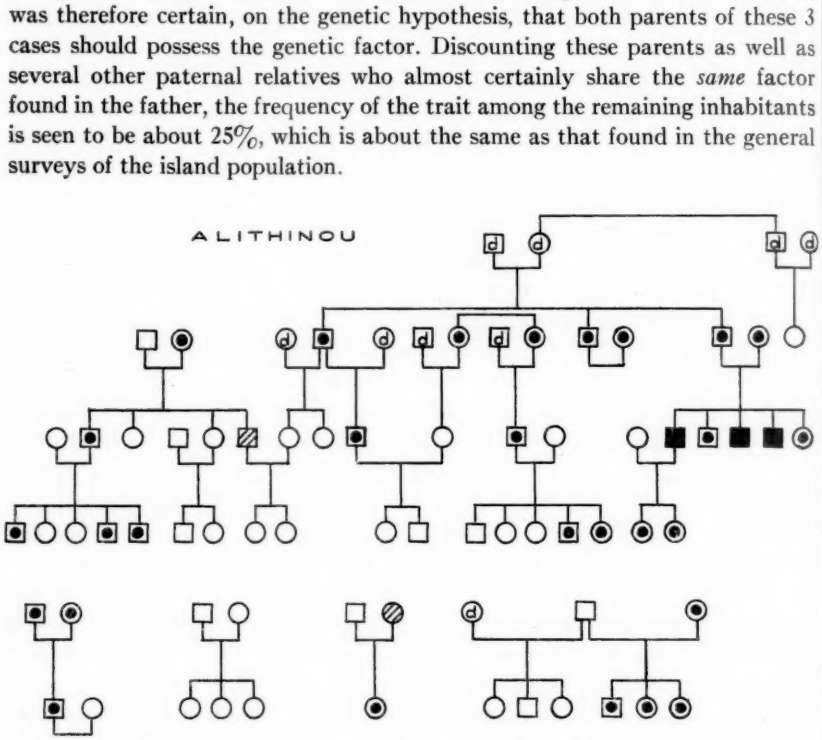

FIG. 2. Distribution of Mediterranean anaemia and trait in the village of Alithinou, Cyprus. Symbolism as in fig. 1.

THE INCIDENCE OF MEDITERRANEAN ANAEMIA IN CYPRUS

Fourteen cases of the disease here reported were seen in a period of nine months. Other cases of the disease were seen, but investigation of them was not possible. In general, I was in contact only with the area around Nicosia, and my knowledge of cases was confined to this region. The pathological laboratory of the Government Hospital, Nicosia, examined the blood of 15 cases of Mediterranean anaemia in the course of the five months from March through July 1946. It is clear that, far from being a rarity, Mediterranean anaemia is a very common disease in Cyprus. An estimate of the total number of cases occurring in Cyprus at any one time must necessarily be a hazardous

one. Adult cases may pass undetected, and many of the villages are not covered by medical supervision which can be relied upon to diagnose the condition. Fawdry (1947), whose experience of the disease was obtained over a period of seven years spent in different parts of the island, considered that one case of the disease could be found in every two villages. This gives a total of about 400 in the island as a whole at any one time, and an incidence of 1 per 1,000 of the population. How he has computed the incidence in the towns such as Nicosia, Famagusta and Limassol, which contain a fair proportion of the population, is not clear. His figure of 400 does give an idea of the problem, however, and in this connection it is of interest to note that Wintrobe (1942) stated that less than a hundred cases had been recorded in the literature. The incidence of the trait is discussed in a separate section.

Regarding the distribution of the cases among the different races of the island, Fawdry (1947) noted that Greeks and Turks were equally affected. This is what would be expected from the incidence of the trait among these two communities. The fourteen cases recorded in this study were all Greek Cypriot, but this was purely fortuitous, since I have seen cases among Turks. Fawdry and I have not seen a case among the Armenian community; but it will be observed that an example of the trait was found in their number among the hundred Cypriots examined for the presence of the trait. Presumably the Armenians are not exempt. Fawdry further noted that males were more often affected than females in the proportion of three to one.

THE GENETICS OF MEDITERRANEAN ANAEMIA

The problem of the transmission of Mediterranean anaemia has been complicated by the fact that whereas the disease was recognised by Cooley in 1927, recognition of the trait or mild form of the disease did not follow until Wintrobe *et al.* (1940) published their paper, though Caminopetros (1938) had recognised changes in red cell fragility in parents of patients with the disease. Moncrieff and Whitby (1934) were the first to suggest a recessive mode of inheritance, but at that time the trait had not been recognised, and parents were regarded as normal. If this had been the case no other conclusion would have been possible. Recognition of the trait in 1940 completely altered the position from a genetic point of view.

In order to determine the nature of the inheritance of Mediterranean anaemia it has been necessary to collect all the reliable pedigrees in the literature together with the pedigrees available from the families in my own series and in the village survey (table 2). Critical analysis of the pedigrees has necessitated exclusion of many families included in previous genetic studies. Though this has reduced the figures available for analysis it has been necessary for various reasons. Thus Caminopetros (1938) produced a family tree with ten cases in four generations. At this time the trait was not fully understood. Strauss *et al.*

TABLE 2. SUMMARY OF PUBLISHED FAMILIES ILLUSTRATING THE INHERITANCE OF MEDITERRANEAN ANAEMIA AND THE CORRESPONDING ERYTHROCYTE ANOMALY OR 'TRAIT'

A. Matings: *Trait* × *Trait*

FAMILY	EXAMINED CHILDREN							
	Disease		Trait		Normal		Total	
	Male	Female	Male	Female	Male	Female	Male	Female
Banton (present study) The "ten families"								
1	1†	–	–	–	–	–	1	–
2	1	1†	–	–	–	–	1	1
3	–	1†	–	1	–	–	–	2
4	1†	1	–	–	–	–	1	1
5	4†	–	1	1	–	2	5	3
6	1†	–	3	–	–	2	4	2
7	1†	–	1	1	–	–	2	1
8	1†	1	–	–	–	–	1	1
9	1	2†	2	1	–	–	3	3
10	1†	–	1	–	–	–	2	–
2*	–	–	2	4	–	–	2	4
9*	–	–	1	–	–	–	1	–
Alithinou village								
1*	–	–	1	–	–	–	1	–
Smith (1943)								
J. A.	2	–	1	–	–	–	3	–
C. A.	–	1	–	–	–	–	–	1
I. C.	–	1	1	–	–	1	1	2
A. DIB.	1	–	1	–	–	–	2	–
J. F.	1	–	1	–	–	1	2	1
D. M.	2	–	1	–	–	–	3	–
A. &. N. P. (twins)	2	–	–	–	–	–	2	–
J. P.	1	1	–	1	–	–	1	2
S. S.	1	1	–	–	–	–	1	1
Valentine & Neel (1944)								
Y.	–	1	1	1	–	–	1	2
Sc.	1	–	1	1	–	–	2	1
Si.	–	1	–	2	1	1	1	4
Wintrobe (1940)								
1	1	–	1	–	–	2	2	2
Totals	24	12	20	13	1	9	45	34
Both sexes	36		33		10		79	

* These families are the result of random selection. All other families recorded were chosen because of a known case of Mediterranean anaemia in at least one child.

† Indicates that the propositus is included in the tally.

B. Matings: *Disease* (*male*) × *Normal* (*female*)

Banton, present study. Family No. 5. Two female children show the trait; no cases of the disease nor normal children.

TABLE 2—*Continued*

C. Matings: *Trait* × *Normal*

This list included families in which (1) both parents were examined. one found to have the trait, the other normal, or (2) only one parent was examined and found normal, yet children are present with the trait. Families with one unexamined parent and one with the trait are excluded, since the unknown parent might have the trait, in which case mating would be of class A.

FAMILY	SEX OF PARENT WITH TRAIT	EXAMINED CHILDREN					
		Trait		Normal		Total	
		Male	Female	Male	Female	Male	Female
Banton (present study) The "ten families"							
1*a*	Female	2	–	–	1	2	1
1*b*	Female	–	–	–	1	–	1
1*c*	Male	–	2	1	1	1	3
2	Male	2	1	1	1	3	2
Alithinou village							
2	Female	1	–	–	2	1	2
3	Female	1	2	–	–	1	2
4	Male	3	–	–	2	3	2
5	Male	–	–	1	1	1	1
6	Male	1	1	1	2	2	3
Smith (1943)							
F. De P.	Female	1	2	–	–	1	2
M. G.	Female	1	–	–	–	1	–
F. R.	Female	1	2	–	1	1	3
A. & J. S. 1	Female	2	–	–	–	2	–
D. S.	Female	2	–	–	–	2	–
A. B.	Male	1	1	–	–	1	1
A. & J. S. 2	Male	–	1	–	–	–	1
Wintrobe (1940)							
2	Male	1	1	–	1	1	2
Valentine & Neel (1944)							
Y. 2	Female	3	1	–	1	3	2
Sal.	Female	2	1	–	–	2	1
Y. 3	Male	1	4	2	1	3	5
Totals	Female	16	8	0	6	16	14
	Male	9	11	6	9	15	20

(1941) described an Italian family in Boston, with ten cases in two generations, but again the trait was not discussed. The families recorded by Damashek (1943) were used by Valentine and Neel (1944), but I have rejected them since his conclusions are open to question. He regarded as normal individuals with fragility end points at 0.24 and 0.16 gm. NaCl.%; these must obviously be regarded with suspicion. The families which have been accepted are those of Wintrobe *et al.* (1940), Smith (1943), and Valentine and Neel (1944).

The parents of patients with Mediterranean anaemia. In all ten families of my series it is noted that both parents of a case of the disease manifest the 'trait'. In the six families in the series recorded by Smith (1943), in which both parents were examined, the trait was again present in both parents in all cases. The same is true in two families of Valentine and Neel (1944), one family of Wintrobe (1940), and four families of Dameshek (1943). Fawdry (1947) had observed this feature in many cases since his attention had been drawn to it by Smith's paper (1943). He had not recorded the number of cases observed, but he gave me details of one such case. He had further noted that when both parents of a case were examined, he had invariably found both to show the trait. There are, therefore, 24 families in which this feature has been recorded, and many more in which it has been observed but not recorded. Smith (1943) refers to one exception he had observed in incomplete studies of one unreported family. It is clear then that as a general rule both parents of a patient with Mediterranean anaemia show the trait, though rare exceptions may occur. The reason for such exceptions will be discussed later.

Offspring of various matings. Where both parents show the trait, it is seen from the analysis that offspring may show either the disease or trait or they may be normal. An excess of males with the disease or trait, and an excess of normal females is noted and will be referred to later. Matings of normal individuals with those showing the trait were found to give rise to offspring who were either normal or showed the trait. This occurred irrespective of which parent showed the trait. In only one mating of a father with the disease and a normal mother were the offspring observed. In this case both children showed the trait. Since the disease is usually fatal in childhood, it is unusual to find cases of the disease having children. In the present series two such cases occur: families 5 and 7 (fig. 1).

Sex incidence of the disease. Analysis of the ten families, including authentic cases of the disease who had died and were not examined by me, show 12 males and 6 females to be affected. Including the figures quoted from other workers, the disease has been found to affect 24 males and 12 females. This predominance in males has also been noted by Fawdry (1947). Though he did not quote his figures, he found the disease to affect males three times more often than females. Why this should occur is not clear. Sex predominance is very common throughout medicine, but apart from its occurrence in such conditions as haemophilia, which is sex linked, the explanation is usually obscure. There is no evidence of sex linkage in Mediterranean anaemia.

Two possible explanations have been put forward. Firstly, the gene, when homozygous, may be more lethal to the female than to the male, and cause intrauterine death. If this were so, it would not affect the sex ratio among normal offspring; one would expect an equal number of normal male and female offspring occurring among the sibs of cases of the disease. Secondly, the penetrance of the gene may be less complete in the female than in the male. In this case, a number of female offspring should appear as normal instead of showing the trait. Analysis of the figures quoted shows one normal male and nine normal female sibs of the cases of the disease. Though the figures are small, they favour the theory of incomplete genetic penetrance of the homozygote in the female.

One might also expect an excess of cases of the trait in males. In matings between parents both showing the trait, 20 males to 13 females showed the trait, and in matings with only one parent involved, 25 males to 19 females were affected. In the latter matings also there were 15 normal daughters to 6 normal sons. These figures are less striking, and once again only small numbers are involved. In Fawdry's survey of 532 school children, quoted elsewhere in this paper, no significant sex preponderance of the trait was observed. Clearly the problem is complex, and larger figures must be obtained before any conclusions can be drawn.

Theories of inheritance. Three theories have been advanced. These have been analysed by Valentine and Neel (1944) and they require further consideration.

1. Mediterranean anaemia is the result of homozygosity for a factor which when heterozygous gives rise to the trait. If the heterozygote were regarded as normal, the disease would be inherited as a mendelian recessive. Before the trait was discovered, the recessive nature of the disease had been recognised by Moncrieff and Whitby (1934), Caminopetros (1938) and Dameshek (1943).

2. Cooley (1941) and Smith (1943) suggested that the severe and mild conditions have the same genetic basis and are due to a dominant factor which is variably expressed. In one person heterozygous for the factor a severe degree of anaemia may develop, whereas in another there may be only slight changes. The difference is presumably due to the effect of environmental and genetic modifiers.

3. McIntosh and Wood (1942) proposed that the disease is caused by the simultaneous presence of two non-allelomorphic dominant factors, one inherited from each parent.

As has been stated, all recorded cases of the disease show both parents affected with the trait, when these have been examined. This is not in keeping with the second hypothesis, since only one parent need be affected to produce the condition. Since matings between 'affected × normal' would be much commoner than between 'affected × affected', the bulk of the cases would be expected to occur as a result of the former type of mating. In McIntosh and Wood's theory two different dominant factors are postulated. Since both parents show the same type of abnormality, one is required to accept the improbable suggestion that two different genotypes produce the same phenotype. The first theory is the only one which will fit the facts.

If one accepts the first theory, then certain proportions of offspring with the disease and with the trait are to be expected. In matings where both parents are heterozygous for the factor, i.e. showing the trait, then the proportion of children with the disease to cases with the trait to normals should be 1:2:1. In the analyses given, the ratio is 36:33:10. In matings between a heterozygote and a normal, the offspring should show the trait or be normal in equal proportions. In the analyses the ratio is 44:21. These figures are not suitable for simple analysis; there are distorting factors which must be taken into consideration. Families with cases of the disease were analysed because these cases presented. This clearly gives a higher proportion of cases of the disease than normal. In the study by Valentine and Neel (1944) Hogben's method (1933) was used to correct for this error. This, however, is not entirely satisfactory, and I am advised that with figures as small as these and with such variable distorting factors detailed statistical analysis would not give conclusive results. It is more important to consider each family analysed and see if any fail to satisfy the conditions laid down for a given hypothesis. By this standard all the families recorded satisfy the first hypothesis.

Variation in severity of the disease and trait. As has been shown already, both the disease and the trait show a wide variation in intensity. Valentine and Neel (1944) considered that the blood picture fell into two fairly well defined groups—the mild case of trait and the severe case. Only relatively few cases were found in between these two extremes. From the experience of cases reported in the literature, it seems that such a distinction is not valid. It would be useful, if one could accept such a hypothesis, since that would fit in well with the theory of heterozygous and homozygous responsibility for the trait and for the disease. It is much more likely, however, that the variation is due either to variable penetrance of the gene or to modifiers, both genetic and environmental. In practice no specific environmental factors could be recognised. In Cyprus the disease was found to affect rich and poor,

town and country dweller alike, and no relationship to any other disease was recognised. It seems likely that the genetic modifiers play the more important role.

This theory offers an explanation of why Smith (1943) found a case of the disease in which only one parent showed the trait. Since the differentiation between the trait and the disease is arbitrary, it is quite possible for genetic modifiers to act in such a way that the factor responsible might produce a severe enough effect even in the heterozygous state to give rise to the disease. It will also explain why cases in the same family usually appear to show the same degree of severity, since the genetic modifiers would be the same in each family.

Expected incidence of Mediterranean anaemia. It has been shown that approximately 20% of the population of Cyprus show the trait of the disease; in other words, one in five of the population is affected. The chance of mating between two such affected persons is therefore 1 in 25. On the theory of inheritance just expounded, one would expect one in four offspring of such a mating to exhibit the disease. This gives an incidence of one in a hundred births. This, however, does not take account of the effect of genetic penetrance and modifiers, nor of intrauterine death of the fertilised ovum. It is also possible that fertilisation itself is affected. It is impossible to compare this figure of one in a hundred with Fawdry's (1947) suggested incidence of the disease of one per thousand in the general population. The result is distorted by the fact that the severe disease is fatal in early infancy or childhood, and therefore the proportion of the general population affected by the disease is still further reduced. Any calculations on this basis could only be made after an extensive analysis of the island to find the true incidence of the trait and the disease, together with accurate observations on the age at death of cases of the disease, and the normal expectancy of life of the Cypriot.

Race limited disease. Mediterranean anaemia is found in a limited region of the Mediterranean seaboard. Greece, Italy, Sicily and Sardinia all show a number of cases as well as the high incidence now recorded in Cyprus. Cases have been reported however from Turkey, Syria and even as far west as Spain. Cases have been recorded in other countries when parents with the trait have emigrated. The majority of such cases have been recorded in America, but some have been seen in England: Moncrieff and Whitby (1934) and Rubie (1948). Apart from this, sporadic cases have been recorded as far afield as India, China and South America. In these cases there was no evidence of the parents being remotely connected with the Mediterranean region. The case recorded by Bywaters (1938) in an English child is an example of this.

The theory of genetic mutation explains these observations satisfactorily. A genetic mutation occurs and if breeding is continued in a localised community then the mutation persists and establishes itself in that community. As Cooley (1941) has pointed out, there is no such thing as a race limited disease. The spread of hereditary disease is limited only by the isolation of the community in which it is found. In the case of Mediterranean anaemia the mutation probably occurred several centuries ago in Greece, and the disease has accordingly spread to neighbouring countries. Cooley (1941) considered that the Mediterranean races show a predisposition to genetic mutations giving rise to blood dyscrasias. The sporadic cases recorded far afield from the Mediterranean are thus the result of a fresh mutation, identical with the one which probably originated in Greece. If, fortuitously, such mutations were given the opportunity to establish themselves, then fresh foci of the disease would occur.

Conclusions. From the data analysed it is clear that Mediterranean anaemia does not follow exactly any given mendelian pattern. This, however, is typical of mammalian inheritance in general. The explanation which fits the facts

most closely is to postulate a mutation of an autosomal gene. This abnormal factor is inherited as a mendelian unit without dominance. In the heterozygous state it gives rise to the trait; in the homozygous state, the disease is produced. Variation in severity of either the disease or the trait is due essentially to the effect of genetic modifiers. These conclusions are similar to those reached by Gates (1946). It should be added that it is exceptional in human genetics to find a condition in which a trait can be recognised with ease and with certainty.

SUMMARY

Ten Cypriot families were investigated showing cases of Mediterranean anaemia, and the haematological data on these individuals are tabulated. Clinical features of the disease as related to genetics are described.

The incidence of the trait of the disease in Cyprus was investigated, and the results of examining 100 adults and 532 schoolchildren are recorded. It was concluded that about 20% of the pupils show the trait. There was no significant difference between the incidence in the two sexes nor between the Greek and Turkish Cypriots. In addition, a survey was also carried out on a small isolated mountain village, wherein the frequency of the trait reaches approximately 50%.

The genetic aspect of the disease was analysed, and results of other workers were quoted. It was shown that cases of the disease almost invariably have parents who both show the trait. No relationship to the ABO blood groups, colour of eyes, or Rhesus factor could be demonstrated. The sex incidence of the disease shows a preponderance among males, but the reason for this is not clear. Theories of inheritance were discussed and it was concluded that the most likely explanation is that which assumes an autosomal gene, which in the heterozygous state gives rise to the 'trait' and in the homozygous state produces the disease. The whole picture, however, is influenced by genetic modifiers.

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Comparative Adaptational, Social, and Psychometric Data on the Life Histories of Senescent Twin Pairs[1]

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In a previous report presented at the fifty-sixth annual meeting of the American Psychological Association (Kallmann & Feingold, 1948), the life histories of senescent twin pairs were explored with respect to the distribution of striking adjustive similarities and dissimilarities as observed in a sample of 2,058 twin index cases over 60 years of age. The emphasis in this analysis was placed on a comparison of intra-pair and inter-group differences in educational, social and occupational background factors, in length of life, and in the variable ability to maintain a state of physical and mental health until and during the period of senescence. While the similarities in socio-economic histories were found to be of nearly the same order of magnitude for one-egg and two-egg groups of twin partners distinguished by survival till senescence, significant differences between the two groups were observed in the total longevity score, in marital fertility, and in the general capacity for adjustment to aging. It was concluded, therefore, that the variable ability to survive, without severe maladjustment, beyond the physiological age of creativeness and reproductivity seemed primarily attributable to genetically determined variations in general biological survival values and adaptational potentialities.

The *organizational scope* of the study was fully explained in previous reports (Kallmann & Sander, 1948, 1949; Kallmann & Feingold, 1949). The most intriguing feature of the investigation was seen in an attempt to procure a longitudinal and controlled series of observational data on adjustment to old age by combining the original twin study method and Weinberg's sampling method, as applied to the study of siblings, with the general principles of a procedure approximating a statewide population census of twins in the older age brackets (Kallmann's twin family method). It may safely be stated now that all the technical and statistical requirements of such a long-term combination procedure have been met successfully by this survey. The available sample has reached a total of over 2,500 senescent twin index cases, while the total period of observation approaches the end of its sixth year.

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Since no essential change has occurred in the *general differential trends* revealed by our previous analysis, it does not seem necessary at this time to recompute detailed comparative data on adjustment or life expectancy for the entire sample. The main justification for this omission may be seen in the fact that approximately one-half of the twin subjects included in the survey, and especially many cotwins in the dizygotic group, are still alive, ranging in age from 61 to 96 years. In general, one-egg twin pairs continue to display marked similarities in physical and mental signs of aging, in the presence or absence of senile enfeeblement or truly psychotic phenomena, in length of life, and in causes of death. For obvious reasons, the converse dissimilarities in two-egg pairs are particularly pronounced in the age group 60–74 years, where they often vary from continued useful activity in one twin to complete invalidism. a senile psychosis, or death in the other twin.

The broad implications of this general observational trend are plainly reflected in a series of illustrative case histories, psychometric test scores, and

TABLE 1. COMPARATIVE DATA ON ADJUSTMENT (PERCENTAGES) IN SAME-SEXED TWIN INDEX PAIRS WITH COMPLETED LIFE HISTORIES

	NO PSYCHOSIS IN EITHER TWIN	DISCORDANCE AS TO PSYCHOSIS	CONCORDANCE AS TO PSYCHOSIS
One-egg pairs	62.1	13.8	24.1
(29)	(18)	(4)	(7)
Two-egg pairs	50.0	46.9	3.1
(32)	(16)	(15)	(1)

special comparative data on the incidence of *senile psychoses* which have been serious enough to require hospitalization.

Crude percentages, that is, percentages uncorrected for differences in age distribution and merely expressing the frequency of institutionalization due to psychotic states of maladjustment which occurred during the period of senescence, are given in table 1 for two comparable groups of same-sexed twin index pairs with completed life histories. Discordance as to the symptomatology of a senile or arteriosclerotic psychosis has so far been observed in 13.8 per cent of deceased one-egg pairs, and in 46.9 per cent of deceased two-egg pairs of the same sex. Beyond question, the difference between the two groups would be much larger, if one would include all those pairs, in whom the cotwin of a psychotic index case is still alive and in good health.

A more comprehensive analysis of age-specific psychosis rates in relation to the degree of consanguinity to a psychotic twin index case over age 50 or 70, respectively, was recently completed for presentation at the International Psychiatric Congress in Paris (Kallmann, 1950). These *expectancy rates* are summarized in table 2 and have been related to all persons over age 44 in the

respective sibships with regard to involutional psychosis, and to all persons over age 59 with respect to senile psychosis. The expectancy for either type of psychosis follows a sliding scale, which is more or less proportional to the degree of blood relationship to the respective type of index case.

It may be concluded, therefore, that one-egg twin partners are more likely than two-egg twins or ordinary siblings to be alike in many of those factors which favor the development of a senile or involutional psychosis. Evidently, the occurrence of either type of psychosis not only presupposes the capacity for survival beyond the beginning of the involutional period and the ability to live through the preceding years of maturity without succumbing to any other kind of psychosis, but also requires a combination of etiological components, which individually would not be sufficient to produce a psychotic reaction syndrome. The most important causative elements apparently include progressive impairment of physical and mental adaptability, an accumulation of emotional strain

TABLE 2. CORRECTED EXPECTANCY RATES (PERCENTAGES) FOR INVOLUTIONAL AND SENILE PSYCHOSES IN PSYCHOTIC TWIN INDEX SIBSHIPS

TYPE OF PSYCHOSIS	HALF SIBLINGS	FULL SIBLINGS	DIZYGOTIC COTWINS	MONOZYGOTIC COTWINS
Involutional	4.5	6.0	6.0	60.9
Senile	—	6.5	8.0	42.8

and insecurity due to increasingly conspicuous signs of aging, and the coexistence of certain basic personality traits modifying adjustive plasticity and the degree of adaptation to involutional changes and senescent decrepitudes.

The extent of *possible adaptational variations*, observable in genetically dissimilar (two-egg) twin pairs despite very similar environmental and existential conditions, may be illustrated by the twin sisters shown in figure 1. They were 80 years old when this photograph was taken, and throughout their lives had differed as much in their personalities and adjustive patterns as they did in their physical appearances and general signs of aging. The younger looking twin, described as sociable, placid and kind, remained active and well-adjusted until she died of a heart attack, a few months before her 83rd birthday. Her taller and more intelligent twin sister, who had always been moody, ill-tempered and vindictive, developed a depressive-paranoid psychosis around the age of 80 and died in a mental hospital three years later.

By contrast, the one-egg A. twins (figure 2), in spite of marked differences in their life histories, remained as indistinguishable during progressive stages of senescence as they had been in childhood and in their earlier years of maturity. They were 18 years old when they were separated through the marriage of one of them to a local farmer. While the married twin continued to live within a radius of ten miles from her birthplace, a small rural community, and raised a large family, the other twin entered a Bible School in her middle twenties and soon left as a missionary for the Orient where she remained until her retirement. She was 65 years old when she rejoined her twin sister, who had meanwhile become a widow. Obviously, it would be rather difficult to find twin partners, who were separated

by a larger distance and under more varied social, cultural and climatic circumstances or who were exposed to greater differences in dietetic and personal living conditions than was true for the A. twins. Nevertheless, when the twin sisters were reunited after 47 years of separation, they were still strikingly similar in physical appearance and were distinguished by an equally serene acceptance of senescence. Such documentary material, showing essential differences between one-egg and two-egg twin index groups in relation to the range of adaptive variations during senium, could easily be multiplied indefinitely.

Equally revealing are the preliminary results of our *psychometric testing program* (Feingold, 1950), which has furnished essential information about the potential effect of genetic factors upon variable changes in intellectual abilities

FIG. 1. Dizygotic twin sisters (X.) at age 80 years.

FIG. 2. Monozygotic twin sisters (A.) at age 67 years.

during senescence. These psychometric data are of general significance for various reasons, but it is not possible here to give more than a brief abstract of the study.

As to the 240 twin index cases who were chosen for this special project from our total series of senescent twin subjects, it may be noted that they formed 75 one-egg and 45 two-egg pairs with a mean age of 69.2 $\pm$ 0.62 (range 60–89 years) and with a sex ratio of 53 male to 67 female pairs. For obvious reasons, the selection of test pairs was limited to white, English-speaking, same-sexed twin partners, who resided in the State of New York and were in an adequate state of physical and mental health. With respect to educational and occupa-

tional background factors, the test pairs approximated a random sample of the general population, except for a certain over-representation of farmers against such typically urban occupations as clerical and factory workers.

The specially designed test battery, with which all of the 120 pairs have been tested at least once, consisted of some of the subtests from the Wechsler-Bellevue Scale—especially Digit Span Forward and Backward, Digit Symbol Substitution, Block Designs and Similarities—the Reproduction of Designs test from the Cornell-Coxe Performance Ability Scale, a Directions test adapted from Price (1933) to measure memory for meaningful verbal material, a paper-and-pencil Tapping test to measure visual-motor coordination, and the Stanford-Binet Vocabulary test (Terman, 1916). Since the main objective of the psychometric program was a study of such changes in mental abilities as may be peculiar to the period of senescence, our battery included a maximum number

TABLE 3. MEAN PSYCHOMETRIC TEST SCORES FOR AGED POPULATION SAMPLES (WITH STANDARD DEVIATIONS)

SAMPLE (INVESTIGATOR)	AGE GROUP (NUMBER OF SUBJECTS)	TEST			
		Digit Span	Similarities	Block Designs	Digit Symbol
Single-born	50–54 yr. (45)	7.7 ± 3.11	8.8 ± 2.94	8.0 ± 2.91	6.8 ± 3.22
(Wechsler)	55–59 yr. (36)	7.5 ± 3.23	7.9 ± 3.38	6.7 ± 3.55	5.9 ± 2.85
Twin pairs Present study	60–89 yr. (190–238)	7.1 ± 2.61	7.5 ± 3.37	6.8 ± 2.74	6.5 ± 2.48

of tests for the measurement of those intellectual functions which may be expected to reveal a decline in correlation with advancing age.

According to the results of the first test round, as tabulated in table 3, it is essential to note that there is no significant difference between the performance of senescent twin subjects and that of a comparable group of single-born persons. If the raw scores for the four tests, which were taken from the Wechsler-Bellevue Scale and weighted in accordance with Wechsler's formulae, are compared with his own findings for the age groups 50–54 and 55–59, the only differential trend observed may be seen in the apparent tendency of the mean scores of aging twin subjects over age 60 to be slightly higher than would be expected on the basis of Wechsler's data.

In an analysis of the *mean raw scores* for the various groups of twin index cases (table 4), the performance of one-egg twins has not been found to differ significantly from that of two-egg twins. However, the scores of female twin subjects tend to be higher on most tests than do those of male twins. The difference in favor of the female sex is significant at the one per cent level of con-

fidence for the Digit Symbol, Block Designs, Directions, and Tapping tests, and does not seem to have been affected materially by the fact that not all the tests listed have been administrable to the entire series of test cases.

As far as differences between corresponding twin partners are concerned

TABLE 4. COMPARISON OF MEAN INDIVIDUAL SCORES (ORIGINAL TESTS) ACCORDING TO SEX AND ZYGOCITY

Mean scores are listed together with their standard errors. Number of subjects for each mean is given under *N*.

TEST	MALE TWINS				FEMALE TWINS			
	Monozygotic		Dizygotic		Monozygotic		Dizygotic	
	N	Mean	*N*	Mean	*N*	Mean	*N*	Mean
Vocabulary	68	28.50 ± 0.58	38	26.26 ± 0.95	82	29.74 ± 0.58	52	27.69 ± 0.80
Digits Forward	68	6.10 ± 0.13	38	5.74 ± 0.15	82	5.80 ± 0.11	52	5.65 ± 0.15
Digits Backward	66	4.30 ± 0.14	38	4.18 ± 0.19	82	4.02 ± 0.10	52	4.04 ± 0.17
Digit Symbol	58	22.93 ± 1.10	24	25.33 ± 1.43	72	32.53 ± 1.16	36	27.90 ± 1.98
Block Designs	64	12.20 ± 0.76	34	12.09 ± 1.11	72	14.06 ± 0.67	36	15.42 ± 1.38
Similarities	64	8.50 ± 0.55	38	7.74 ± 0.65	80	9.82 ± 0.50	48	8.58 ± 0.68
Directions	28	14.96 ± 1.12	14	12.78 ± 2.24	50	19.70 ± 1.11	26	17.46 ± 1.21
Tapping	64	66.36 ± 2.03	34	56.18 ± 2.76	74	68.90 ± 1.88	44	68.68 ± 2.58
Reproduction of Designs	22	8.64 ± 0.58	4	6.50 ± 1.04	44	10.66 ± 0.65	20	9.25 ± 0.97

TABLE 5. COMPARISON OF MEAN INTRA-PAIR DIFFERENCES ACCORDING TO SEX AND ZYGOCITY

Mean intra-pair differences and their standard errors have been computed separately for monozygotic and dizygotic male pairs and monozygotic and dizygotic female pairs. Number of pairs for each mean is listed under *N*.

TEST	MALE PAIRS				FEMALE PAIRS			
	Monozygotic		Dizygotic		Monozygotic		Dizygotic	
	N	Mean	*N*	Mean	*N*	Mean	*N*	Mean
Vocabulary	34	2.47 ± 0.35	19	3.89 ± 0.62	41	2.22 ± 0.29	26	4.77 ± 0.87
Digits Forward	34	1.09 ± 0.15	19	1.05 ± 0.23	41	0.83 ± 0.11	26	1.08 ± 0.17
Digits Backward	33	0.91 ± 0.13	19	0.89 ± 0.17	41	0.73 ± 0.11	26	1.15 ± 0.21
Digit Symbol	29	5.34 ± 0.80	12	6.92 ± 1.31	36	4.42 ± 0.62	18	9.25 ± 1.66
Block Designs	32	3.59 ± 0.48	17	6.88 ± 0.87	36	3.17 ± 0.50	18	6.17 ± 1.37
Similarities	32	2.69 ± 0.54	19	2.95 ± 0.69	40	2.45 ± 0.38	24	4.17 ± 0.75
Directions	14	4.64 ± 0.96	7	6.43 ± 2.63	25	4.92 ± 0.80	13	4.62 ± 1.59
Tapping	32	8.47 ± 1.18	17	18.47 ± 2.77	37	11.65 ± 1.13	22	13.82 ± 2.20
Reproduction of Designs	11	1.82 ± 0.46	2	3.00 ± 0.00	22	2.68 ± 0.54	10	3.90 ± 0.79

(table 5), it is of particular interest that the *mean intra-pair differences* in test scores measuring abstract intellectual functions are significantly smaller in one-egg than in two-egg pairs of female twins, the differences between the female groups being significant at the one per cent level of confidence for the Vocabulary, Digits Backward, Digit Symbol, Block Designs, and Similarities tests. A

similar trend toward inter-group differences in within-pair variance is noticeable between the two male zygocity groups, but the given differences are not significant at the one per cent level. This discrepancy between the sexes may indicate that certain intellectual changes in senescent males precede those observable in aging females. However, the number of male two-egg test pairs available for this analysis does not seem sufficient to permit far-reaching conclusions without extensive control investigations of this rather important biological problem.

It may be mentioned in this connection that retests, administered to one-half of the original test pairs after an interval of approximately one year and compared with the original test scores by means of analysis of variance, revealed no significant changes in any of the tests for any of the four groups analyzed. The test-retest intra-class correlations range from 0.903 (Directions test) to

TABLE 6. COMPARISON OF INTRA-PAIR DIFFERENCES ACCORDING TO ANALYSIS OF VARIANCE

TEST	F_1		F_2	F_3
	Monozygotic	Dizygotic		
Vocabulary	10.16†	3.03†	1.10	3.68†
Digits Forward	2.13†	1.03	1.54	1.34
Digits Backward	2.75†	1.85*	1.12	1.67*
Digit Symbol	9.94†	2.93†	1.24	2.73†
Block Designs	6.18†	2.67†	1.38	3.20†
Similarities	4.94†	2.10†	1.28	1.84*
Directions	4.98†	2.28*	1.28	1.71
Tapping	5.90†	2.49†	1.01	2.35†
Reproduction of Designs	5.06†	2.55	1.01	1.97

F_1 = between pair/within pair variance.
F_2 = ratio of between-pair variances in two zygocity classes.
F_3 = ratio of within-pair variances in two zygocity classes.

* Significant at 5% level.
† Significant at 1% level.

0.996 (Vocabulary test) and may be taken as an indication of the usefulness of the original test scores for comparison with the results of future follow-up studies.

Another interesting finding is that those tests which measure specific elements of *memory function* such as simple recall of recent material (Digit Forward, Directions, Reproductions of Designs) fail to discriminate—as is shown in table 6—between the one-egg and two-egg groups of test pairs in either sex.

Unfortunately, no comparable psychometric data seem to be available in the literature with respect to tests measuring various aspects of recall (cf. Burgess & Cottrell, 1939; Dahlberg, 1948; Stern, 1948; Popenoe & Johnson, 1923; Hamilton, 1929). On the basis of our test series it would seem worth recording, however, that no significant effect of genetic factors has been observed in relation to the ability to recall digits and meaningful verbal or visual material,

by a larger distance and under more varied social, cultural and climatic circumstances or who were exposed to greater differences in dietetic and personal living conditions than was true for the A. twins. Nevertheless, when the twin sisters were reunited after 47 years of separation, they were still strikingly similar in physical appearance and were distinguished by an equally serene acceptance of senescence. Such documentary material, showing essential differences between one-egg and two-egg twin index groups in relation to the range of adaptive variations during senium, could easily be multiplied indefinitely.

Equally revealing are the preliminary results of our *psychometric testing program* (Feingold, 1950), which has furnished essential information about the potential effect of genetic factors upon variable changes in intellectual abilities

FIG. 1. Dizygotic twin sisters (X.) at age 80 years.

FIG. 2. Monozygotic twin sisters (A.) at age 67 years.

during senescence. These psychometric data are of general significance for various reasons, but it is not possible here to give more than a brief abstract of the study.

As to the 240 twin index cases who were chosen for this special project from our total series of senescent twin subjects, it may be noted that they formed 75 one-egg and 45 two-egg pairs with a mean age of 69.2 $\pm$ 0.62 (range 60–89 years) and with a sex ratio of 53 male to 67 female pairs. For obvious reasons, the selection of test pairs was limited to white, English-speaking, same-sexed twin partners, who resided in the State of New York and were in an adequate state of physical and mental health. With respect to educational and occupa-

tional background factors, the test pairs approximated a random sample of the general population, except for a certain over-representation of farmers against such typically urban occupations as clerical and factory workers.

The specially designed test battery, with which all of the 120 pairs have been tested at least once, consisted of some of the subtests from the Wechsler-Bellevue Scale—especially Digit Span Forward and Backward, Digit Symbol Substitution, Block Designs and Similarities—the Reproduction of Designs test from the Cornell-Coxe Performance Ability Scale, a Directions test adapted from Price (1933) to measure memory for meaningful verbal material, a paper-and-pencil Tapping test to measure visual-motor coordination, and the Stanford-Binet Vocabulary test (Terman, 1916). Since the main objective of the psychometric program was a study of such changes in mental abilities as may be peculiar to the period of senescence, our battery included a maximum number

TABLE 3. MEAN PSYCHOMETRIC TEST SCORES FOR AGED POPULATION SAMPLES (WITH STANDARD DEVIATIONS)

SAMPLE (INVESTIGATOR)	AGE GROUP (NUMBER OF SUBJECTS)	TEST			
		Digit Span	Similarities	Block Designs	Digit Symbol
Single-born	50–54 yr. (45)	7.7 ± 3.11	8.8 ± 2.94	8.0 ± 2.91	6.8 ± 3.22
(Wechsler)	55–59 yr. (36)	7.5 ± 3.23	7.9 ± 3.38	6.7 ± 3.55	5.9 ± 2.85
Twin pairs Present study	60–89 yr. (190–238)	7.1 ± 2.61	7.5 ± 3.37	6.8 ± 2.74	6.5 ± 2.48

of tests for the measurement of those intellectual functions which may be expected to reveal a decline in correlation with advancing age.

According to the results of the first test round, as tabulated in table 3, it is essential to note that there is no significant difference between the performance of senescent twin subjects and that of a comparable group of single-born persons. If the raw scores for the four tests, which were taken from the Wechsler-Bellevue Scale and weighted in accordance with Wechsler's formulae, are compared with his own findings for the age groups 50–54 and 55–59, the only differential trend observed may be seen in the apparent tendency of the mean scores of aging twin subjects over age 60 to be slightly higher than would be expected on the basis of Wechsler's data.

In an analysis of the *mean raw scores* for the various groups of twin index cases (table 4), the performance of one-egg twins has not been found to differ significantly from that of two-egg twins. However, the scores of female twin subjects tend to be higher on most tests than do those of male twins. The difference in favor of the female sex is significant at the one per cent level of con-

fidence for the Digit Symbol, Block Designs, Directions, and Tapping tests, and does not seem to have been affected materially by the fact that not all the tests listed have been administrable to the entire series of test cases.

As far as differences between corresponding twin partners are concerned

TABLE 4. COMPARISON OF MEAN INDIVIDUAL SCORES (ORIGINAL TESTS) ACCORDING TO SEX AND ZYGOCITY

Mean scores are listed together with their standard errors. Number of subjects for each mean is given under *N*.

TEST	MALE TWINS				FEMALE TWINS			
	Monozygotic		Dizygotic		Monozygotic		Dizygotic	
	N	Mean	*N*	Mean	*N*	Mean	*N*	Mean
Vocabulary	68	28.50 ± 0.58	38	26.26 ± 0.95	82	29.74 ± 0.58	52	27.69 ± 0.80
Digits Forward	68	6.10 ± 0.13	38	5.74 ± 0.15	82	5.80 ± 0.11	52	5.65 ± 0.15
Digits Backward	66	4.30 ± 0.14	38	4.18 ± 0.19	82	4.02 ± 0.10	52	4.04 ± 0.17
Digit Symbol	58	22.93 ± 1.10	24	25.33 ± 1.43	72	32.53 ± 1.16	36	27.90 ± 1.98
Block Designs	64	12.20 ± 0.76	34	12.09 ± 1.11	72	14.06 ± 0.67	36	15.42 ± 1.38
Similarities	64	8.50 ± 0.55	38	7.74 ± 0.65	80	9.82 ± 0.50	48	8.58 ± 0.68
Directions	28	14.96 ± 1.12	14	12.78 ± 2.24	50	19.70 ± 1.11	26	17.46 ± 1.21
Tapping	64	66.36 ± 2.03	34	56.18 ± 2.76	74	68.90 ± 1.88	44	68.68 ± 2.58
Reproduction of Designs	22	8.64 ± 0.58	4	6.50 ± 1.04	44	10.66 ± 0.65	20	9.25 ± 0.97

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Mean intra-pair differences and their standard errors have been computed separately for monozygotic and dizygotic male pairs and monozygotic and dizygotic female pairs. Number of pairs for each mean is listed under *N*.

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similar trend toward inter-group differences in within-pair variance is noticeable between the two male zygocity groups, but the given differences are not significant at the one per cent level. This discrepancy between the sexes may indicate that certain intellectual changes in senescent males precede those observable in aging females. However, the number of male two-egg test pairs available for this analysis does not seem sufficient to permit far-reaching conclusions without extensive control investigations of this rather important biological problem.

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although such factors evidently continue during senescence to play an important part in the determination of those intellectual functions, which are concerned with vocabulary knowledge, formation of new associations, and nonverbal intelligence.

The extent of genetically produced variations in intellectual abilities during senescence may be illustrated graphically for the Vocabulary test in a frequency polygon (figure 3), in which the intra-pair differences in original test scores for the two zygocity groups have been plotted against cumulative frequencies (in percentages). There is no overlap between the two curves, and the probability that the inter-group discrepancy in the mean intra-pair differences (2.33–

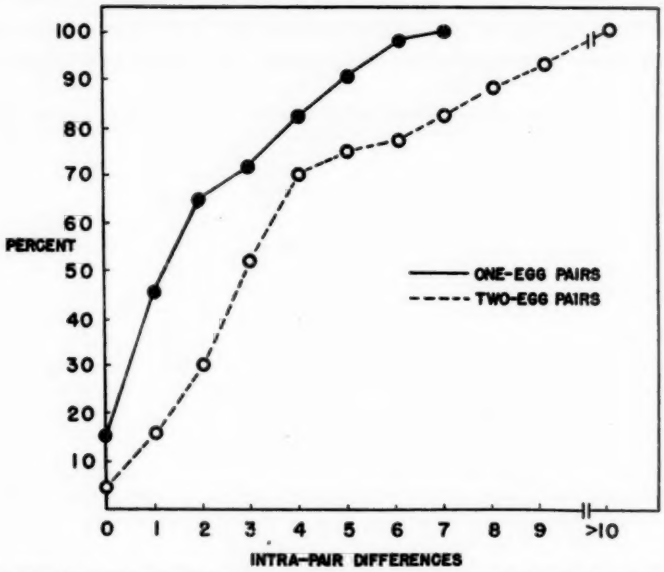

FIG. 3. Cumulative frequency distribution of intra-pair differences in Vocabulary test scores.

4.40 words) may be due to chance is less than 0.001. It may also be noted in this connection that any dissimilarities in schooling which existed between the members of some of our test pairs have not been found to be manifested in measurable differences in test performance after an interval of 35 to 65 years following the termination of formal education.

In conclusion it may be said, therefore, that the similarities in the intellectual performances, adaptive potentialities and adjustive patterns of senescent one-egg twins generally exceed those observed in two-egg pairs. The manner in which genetically determined variations in aging and longevity correspond with those in intellectual and adaptational abilities is conclusive evidence of the considerable extent to which genic elements influence a person's variable

capacity for maintaining a state of physical and mental health throughout life.

It seems justified to infer that the ability to survive until, and to adjust to, the period of senescence is part of the *normal* equipment of man. This ability is apt to display many graded variations within the limits of normalcy, apparently due to the additive effects of a great number of gene units.

Severe maladjustment to aging, resulting in the symptomatology of an *involutional or senile psychosis*, seems to depend on a *combination* of etiological components—including age-susceptible personality traits, declining adaptational plasticity, increasing emotional and socio-economic insecurity—which may be expected to coexist more frequently in genetically alike persons (one-egg twins) than in genetically unlike persons (two-egg twins).

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BOOK REVIEWS

Population Genetics and Animal Improvement

By I. M. LERNER (Department of Poultry Husbandry, University of California, Berkeley 4, Calif.) Cambridge: The University Press. Pp. xviii + 342. $5.50.

THE student of human genetics may feel that he has little need to concern himself with a book whose avowed aim is the examination of the effects of selection for a quantitative trait in a domestic animal. Dr. Lerner's book, however, has much to interest him, for it contains one of the most comprehensive accounts yet published of the implications of Mendelian genetic theory for the inheritance of a quantitative character.

This book naturally invites comparison with Mather's *Biometrical Genetics*. Both are based upon the concept of a polygenic determination of metrical characters, functioning in accordance with the usual laws of particulate inheritance but involving an unspecified large number of genes whose individual effects are small. The theoretical study of components of variance that formed Mather's main theme is perhaps more directly relevant to human genetics. Lerner writes almost exclusively of factors influencing egg production in poultry, and considers various problems of selection for improved production with strong emphasis on their 'operational' aspects; that is to say, he is not content to make purely theoretical comparisons between the advances achieved by alternative systems of mating and selection, but he evaluates these in terms of their over-all cost to the breeder in time and flock-size. His book is not easy to read, for the underlying mathematical structure is complicated and is presented only in outline, but its outlook is essentially practical. The primary importance of the policy adopted by the breeder may obscure the relevance of Lerner's exposition to populations not experiencing any imposed breeding policy, but in fact Lerner's analysis is likely to be of wider application. The domestic fowl appears to be one of the most suitable of animals of economic importance for intensive genetic study, because of both the sizes of progenies that can be raised and the relative shortness of generations. Although a proper understanding of quantitative inheritance in man is not likely to be attained for many years yet, at least by conventional methods of study, the methods of its attainment will probably derive from those whose value is proved in other species; Lerner's analysis of the factors influencing egg-production is an excellent example of what can be achieved by a combination of modern statistical techniques.

After a survey of the history of the scientific study of egg-production, Lerner discusses the question of choosing a suitable production index; this is necessarily a little arbitrary in definition, but a proper regard is had to its operational use in a breeding programme. The University of California flock of White Leghorns, on which almost all the numerical work of the book is based, is next described, with a full account of the breeding policy used since its foundation in 1933. An important chapter on the fundamental postulates used in applied population genetics discusses clearly the effect of mating systems and gene frequencies on the relationship between genotypic and phenotypic variations; this is followed by a brief but clear explanation of coefficients of inbreeding and genetic relationship. Subsequent chapters are more directly related to egg-production—its heritability, the principles to be adopted in selecting for its increase, the rate of genetic advance, systems of mating, and the evidence on which selection is to be based—all plentifully illustrated from the University

of California flock. Two chapters are devoted to consideration of inter-relationships between different phenotypic characteristics, desirable and undesirable, and the possible benefits of using a composite selection index. A brief chapter on miscellaneous topics and another on problems for the future complete a valuable book.

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Genetics and the Races of Man

By WILLIAM C. BOYD (Department of Immunochemistry, Harvard University, Cambridge, Mass.) Boston: Little, Brown & Co., 1950. Pp. xvii + 453, with 52 text figures. $6.00.

PHYSICAL anthropology is much older than the re-discovery of mendelism; already when genetics was becoming a science, anthropology had accumulated large collections of quantitative observations. The early controversies between the biometricians and the mendelians largely passed anthropology by, and for another forty years and more anthropologists continued to amass metric data at an increasing rate without, perhaps, fully realising the limitations of such material.

Meanwhile, the science of blood group anthropology was founded in 1918 by the Hirszfelds and subsequently carried on by numerous workers all over the world. Dr. W. C. Boyd was almost unique among them, however, in taking a world-wide view of the subject, and he put everyone in his debt by his monumental and comprehensive compilation and systematization of the work published up to 1938. Here henceforth was a rich source into which many workers could and did dip for support for their varied racial theories; but this at least was a mass of data which no anthropologist could ignore, and when, in addition to the ABO groups, the Rhesus factor and the other 'new' blood groups began to show frequencies varying widely from one population to another most physical anthropologists began to take an active interest. Not all, however, who have applied blood groups to racial studies have done so with adequate genetical understanding, nor have the technical limitations of the serology involved always been appreciated. It therefore needed the efforts of someone with an adequate understanding of anthropology, of genetics and of serology, and familiar with the existing data, to show to workers in each of these sciences, and to scientists generally, the great contribution which genetics, and especially blood groups, had made to anthropology, and the much greater contribution which they could make in the future. Other than Dr. Boyd himself, few, if any, workers would have been competent to make this synthesis, and it is a matter for great satisfaction that he has seen fit to do so.

The book begins with an account of popular views and prejudices regarding racial distinctions, and the author demonstrates the inadequacy not only of these views but of the classical criteria of anthropology and of all classifications not firmly based on genetics. He then compresses into one chapter an account of the science of genetics. This is on the whole very clear, but the account of crossing-over is quite inadequate and would be incomprehensible to anyone new to the subject. If, as we hope, a second edition of the book is called for, this section should be rewritten and greatly expanded, preferably with diagrams drawn expressly for the purpose.

The succeeding chapters trace the various effects of the environment and of genetical mechanisms in the moulding of the species of living creatures in general. A chapter on the

influence of geography on human racial distribution leads up to one on the central theme of the book, the concept of race. Here the author emphatically rejects all those theories which would give an emotional rather than a scientific value to the term, and he clearly has considerable sympathy with those persons who would abandon altogether the use of this much-abused word. He concludes, however, that the concept of race still has some value if it is regarded as applying to a constellation of characters no single one of which is to be regarded as a *sine qua non*.

The remainder of the book is devoted to the laying down of the broad lines of an analysis of mankind in terms of genetical differences and especially of the blood groups. A brief but clear account of the serology and genetics of the A_1A_2BO, Rh, and MN blood group systems is followed by a description of the world distribution of the genes involved. Here the author interposes an account of an imaginary world in which blood group genes produce directly visible somatic effects. This must be read very carefully if the reader is not to be left in a state of mental confusion; it might have been preferable to omit it.

Dr. Boyd has used in these chapters only a fraction of the blood group data already compiled by himself and of the data which have since accumulated. To deal with all this material in any detail would require another book as large as the present one. In the short interval since the book was written much work of the highest importance has been published, and were it being written now it would be necessary to give fuller details of the distribution of the Rh, MNS, and P systems. Even the Duffy system, the discovery of which was only announced in 1950, shows promise of having as great a value in anthropology as is possible with a two-gene system, since the few observed frequencies of the antigen are widely spaced over the whole range from zero to 100 per cent.

Two more chapters follow, one on other human genes, and one on incompletely analysed characters. Here again recent work, some of it by the author himself, has led to great advances in the short interval since the book was written. Finally an attempt is made to reconstruct the history of man on a genetical basis and to predict his future development.

There is a most useful series of appendixes on statistical methods. Each chapter has a good but not exhaustive list of references ending, with a few exceptions, at 1947. The indexing is adequate, the printing clear and the binding sound. There are very few misprints.

This is a book which ought to be in the hands of all geneticists, blood-group serologists and anthropologists. To each it will be a rich source of new ideas. The geneticist will find mapped out a new territory for the application of his principles; the serologist a new field for his techniques. But the anthropologist will find a completely new anthropology, one already foreshadowed by the leaders of the science but not yet incorporated into its body; though this development must come if physical anthropology is to remain one of the natural sciences.

The book is not and does not pretend to be a complete source book of references. Those who have read it and wish to chase the many hares which it has started in their minds are recommended to follow some of them through the pages of the proceedings of the Cold Spring Harbor Symposium of 1950 on anthropology and genetics. Equally, those who wish to trace a connected theme in the varied papers of the Symposium should read the book.

But this is not a book for specialists only. Anyone with a scientific background should be able to follow the arguments and will almost certainly find them to be of absorbing interest. Nor is this a political treatise; but the acceptance of its principles by politicians might in the past have prevented and may in the future prevent a great many blunders and tragedies.

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Tooth Size and Occlusion in Twins

By ANDERS LUNDSTRÖM (State Institute of Human Genetics, Uppsala, Sweden). Basle, Switz. and New York: S. Karger Verlag, 1948. Second Edition. Pp. 203, with 29 text figs. Swiss Fr. 16.

THE TWIN METHOD is here used to analyse the relative importance of genetic and non-genetic factors in tooth-size, tooth-space and occlusion, special attention being given to the variability of normal occlusion. Following Dahlberg's methods the distinction is made not between the effects of heredity and environment, but between heredity and non-heredity, the latter including both environmental and internal factors. The sample analysed consists of 100 pairs of monozygotic and 102 pairs of like-sexed dizygotic twins.

The main criticism of the study concerns the method of diagnosis of zygosity, which is based on "the general similarity of the twins," including eye-colour and ear-shape, but making no use of the newer valuable indices, such as blood groups or the analysis of dermal configurations. Lundström admits that his method "may cause a few mistakes," but the reviewer feels that the error in this regard may be a serious one. Out of the 100 pairs of monozygotic twins used in the study, there were 5 pairs included who "were generally not mistaken for each other," but between whom the author could not distinguish. There were also 3 pairs who could not be examined at the same time, but who according to information were "usually mistaken for each other," another 2 pairs about whom there was no information except that they were usually mistaken for each other; and finally 1 pair who were usually not mistaken, but who seemed difficult to distinguish, except for dissimilarities in the structure of their ears. This means that there was some doubt concerning the zygosity of at least 11% of the monozygotic twins, and, with a possible error of even less than this the careful statistical analysis which follows loses much of its point.

The widths of the teeth, their positions in the jaws and the occlusion of the jaws were carefully determined from a series of measurements taken on plaster-models. The results indicate that the genetic factors are of relatively great significance in the variability of tooth- and jaw-size. Although the investigation refers particularly to normal occlusion, it is anticipated that for malocclusion heredity will also be the most important factor, provided other factors such as trauma have been eliminated.

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Genetics in Ophthalmology

By ARNOLD SORSBY (Royal College of Surgeons of England, London W.C. 2). St. Louis: C. V. Mosby & Co., and London: Butterworth & Co., 1951. $9.50.

NEARLY thirty years has gone by since such a major work on heredity in Ophthalmology has appeared. Sorsby's book compares favourably with the Nettleship Memorial Volume of the *Treasury of Human Inheritance*, or with Franceschetti's work in the *Kurzes Handbuch der Ophthalmologie*, or with Waardenburg's *Das menschliche Auge und seine Erbanlagen.*

Although possibly not as extensive as some of those older works, the present text, by the author's wise choice of material from the literature and by his careful assessment of the various theories and opinions, is, to the clinician, more readable and more useful.

The book is of convenient size, well bound. The paper is semigloss, exhibiting a clear type and faithfully accepting zinc plate and half tone illustrations. Coloured plates are bound into the volume on slightly heavier, higher gloss paper, and satisfactorily reproduce the originals. There are 233 figures, including family trees and coloured or black-and-white illustrations of disease. Throughout the text, and appended to the illustrations, mention is made of appropriate references in the literature. At the end of the book a bibliography is presented, one of the most valuable features of which is the careful selection of only the important and useful references. The index, both by authors and subjects, is adequate.

The book is organized in a simple, and pleasing, fashion. There are only three major divisions: theoretical considerations, isolated ocular disease, generalized disorders with ocular aspects.

"Theoretical Aspects" deals with our basic knowledge in the field of heredity, particularly as applies to ophthalmology. Much of this material could be found in standard texts on genetics. However, in this book, examples from the ophthalmic literature are used to illustrate many of the well recognized principles of genetics. The major types of inheritance are all adequately depicted by examples from ocular diseases. Such subjects as mutants, the control of genetic disease, are discussed by an ophthalmic approach which impresses the practical importance of such theoretical aspects.

"Isolated Ocular Diseases" is a large section, containing seven chapters, and 127 pages of the book's 242 pages. Among the subjects discussed under the title of "The Globe as a Whole" are two important problems, heredity in glaucoma and heredity in myopia. He weighs the evidence concerning heredity as a factor in glaucoma, points out the importance of this etiology, but also points out fallacies into which the literature may lead us. The discussion of the hereditary factors in ametropia is a model of careful analysis and conservative estimate. The presence of heredity as a factor and the difficulty of assessing that factor are well brought out. Heredity as a factor in squint is worthily described. This subject is particularly interesting in view of recent work by Fink, and others, on anomalies of the check ligaments.

The corneal dystrophies are thoroughly inspected. The combined description of the clinical and hereditary types is most helpful. The large section devoted to hereditary cataract brings forward a subject the clinician is prone to forget. The degenerations of the retina and choroid are extensively described. One of the pleasing features of this part of the book is the adequate, but not too detailed, organization of this subject.

"Generalized Disorders with Ocular Aspects" is a most valuable section of the book. The author describes eye changes in some metabolic hereditary diseases, in some other systemic disorders, and in some syndromes. The organization of this section is indeed difficult because these subjects are diffuse, advancing rapidly, and liable to take new turns which at present are not visible. Sorsby has organized this material so that it is presented in a logical sequence, not confused by many disconnected facts. The presentation of various hereditary abnormalities of the skeletal system is particularly worthy.

If you are interested in this subject, or are practicing ophthalmology, you should have this book.

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A Study of Epilepsy in Its Clinical, Social, and Genetic Aspects

By CARL HENRY ALSTRÖM (Laboratory for Human Genetics of the Psychiatric Clinic, Caroline Institute, Stockholm). Copenhagen: *Acta Psychiatrica et Neurologica* Supplementum 63; Ejnar Munksgaard, 1950. Pp. 284, with 7 figures and 23 tables. Price 20 Swedish Crowns.

THE investigation reported in this monograph was carried out during the years 1945 to 1950 on patients who were examined for epileptic symptoms during the period 1925 to 1940 at the Neurological Clinic of the Caroline Institute at the Serafimer Hospital in Stockholm. Its objective, as the title implies, was to evaluate the clinical and social prognosis of non-institutionalized patients suffering from epilepsy and to determine the role of heredity in the cause of the disease.

In accordance with the thoroughness and care that are usual in Swedish investigations of this type, all patients who were followed were visited at their homes and interviewed and re-examined. At this time, all available siblings, children, and parents were also examined and interviewed; information about those who were not available was obtained by questioning the relatives and from medical records or other official records. For all except seventy-five of the patients who were re-examined, the follow-up was done by Alström or his assistant; in these 75 cases, the follow-up was done by physicians following his instructions.

The results of the investigation are reported under 6 chapter headings as follows: I. The present series. II. Clinical grouping and prognosis. III. Social factors. IV. The genetic investigation. V. A brief summary of the development of the concept of epilepsy. VI. The Swedish law prohibiting the marriage of epileptics.

On the basis of the original examination, in the follow-up study the cases were divided into 3 groups according to the "cause," namely, unknown, probable, and known, (U, P and K respectively), depending upon whether or not a "cause" for the epilepsy could be determined. Alström emphasizes that the group of cases classified as unknown is the same as that which is called idiopathic or genetic in other clinics. Of 897 cases in which the patients were followed, 606 (68 per cent) were classified U, 150 P, and 141 K. Alström's general conclusion, which is supported by his data, is that there are no essential differences among the 3 groups. The differences that do exist tend to show a better prognosis for the U group, that is, the so-called idiopathic or genetic group, with respect to psychic change, recovery from seizures, and mortality. Alström strongly criticises the use of the terms "idiopathic" and "symptomatic" because they imply a basic difference between the 2 groups of epileptics, and he urges that they be abandoned.

He casts doubt upon Lennox' statement that "idiopathic (genetic)" epilepsy is more frequent among females by showing that the sex ratio is equal in the U group and that an excess of males occurs only in the P and K groups. He demonstrates that this excess is due to a greater risk of head injuries among males.

There is a greater frequency of mental change in the P and K groups than in the U group (47 per cent as compared to 21 per cent), but in each case only about a third of those who suffered mental changes show the 'epileptic' type of deviant personality. Alström contends that the 'epileptic type of deviant personality' is a misnomer and should be abandoned.

The frequency of marriage among the mentally unchanged was only slightly below that of the general population even when the onset of epilepsy occurred before the patient was

twenty years old. The fertility of these marriages, however, is only about 50 per cent of that of the general population.

Using Stromgren's weighting system to take into account the variability in age of onset, Alström has calculated a useful table of morbidity risk against age. This table shows that by twenty-two years, only 50 per cent of the risk has been passed, and that less than 65 per cent is passed by 30 years of age. On the basis of weighted values which correct for age differences, he calculated the frequency of epilepsy among the parents, sibs, and children of the probands in each of the 3 groups, U, P and K, and showed that within statistical limits (which unfortunately are quite wide) the 3 groups are consistent and that the frequency of epilepsy among the 3 sets of relatives is the same, within statistical limits (which again are very wide); about 1.5 per cent. However, in all 3 groups the frequency is highest among the patients' children (average is 3 per cent), and one wonders if this indicates a bias in the weighting system because not enough cases with early onset were included among the probands or if with a larger sample a real difference would be shown to exist. It is unfortunate that no tables showing the distribution of the age at onset among the patients and the age distribution of the parents, sibs and children of the patients are given. Such tables would have been most useful to those interested in using the data themselves.

Alström introduces his genetic analysis with an excellent discussion of heredity and environment. While none of it is new to geneticists, it is very valuable to have such a clear presentation of the material in a medical publication. He then proceeds to rule out any simple pattern of inheritance as a factor in the cause of epilepsy in the group as a whole. He continues his argument to rule out a multiple factor hypothesis by stating that no such situation exists for epilepsy in other mammals and by arguing that a threshold phenomenon cannot exist since convulsions can be induced in everyone by one means or another. The former argument is factually incorrect, and the latter is equivalent to saying that mutations reducing viability (semilethals for example) cannot exist because everyone can be made to die.

The author criticises Conrad's work on twins because he found an excess of dizygotes and because he used institutionalized patients. He criticises Lennox' work because Lennox found too few dizygotes among the noninstitutionalized twins he studied. But Alström overlooked the most striking feature of these studies, namely, the high degree of concordance that each of these workers found among monozygous twins suffering from so-called idiopathic epilepsy and the much lower concordance in other groups. He failed to note also the close agreement in the frequencies found by these two workers.

With the exception of eight families, Alström considers genetics as unimportant in the production of epilepsy. However, by using his total data we find that the frequency of epilepsy among the sibs of the probands is 0.9 per cent when neither parent is epileptic and 5.1 per cent when one parent is epileptic. It seems that this, along with Lennox' electroencephalographic work and the work on twins, suggests very strongly that genetics does play an important, if unclear, role in the production of epilepsy.

Space does not permit an extensive discussion of Alström's criticisms of Lennox' work, but it should be pointed out that Alström has lifted some sentences out of the context and used them to criticise Lennox and the entire concept of a genetic component in the production of epilepsy. It is most unfortunate that Alström did not undertake sufficient electroencephalographic work to test Lennox' hypothesis. The data of the one family for which electroencephalograms were available for all members does not contradict Lennox' hypothesis and in fact lends further support to it.

Because so much time, effort and thought have been devoted to this work, we are sorry to have to adopt such a negative attitude toward it. We are particularly distressed to have

to point out the following fundamental weakness in the study. During the period 1925 to 1940, 1,472 epileptic patients, none of whom were institutionalized, were seen at the clinic. Alström was able to follow only 897 (60.9 per cent) of these. More than 250 were lost because of faulty addresses, and 319 more were lost for one of the following reasons: (1) patient was away on a holiday or for another reason at the time of the home visit; (2) patient lived too far away from the planned route of travel, and (3) some patients were missed because of the time limit set to the investigation. No statement is made with regard to how many patients fell into each of these categories. The 39.1 per cent of the original total of patients who were not followed are in no way considered in the report. It would have been very helpful to have had a comparison of the original diagnoses in these cases with that in the 60.9 per cent of cases in which the patients were followed. Alström notes that, "It was necessary for financial reasons to limit the investigation. This limitation mainly operated in the case of the out-patients as, from a point of view of the examination technique, this was a very heterogeneous series and far from in the same class as the other two categories of patients (in-patients of the clinic and private patients of the Professor of Neurology). Difficulties were often encountered in the form of incomplete addresses." Hence there remains the possibility if not the probability that the conclusions of this study rest on a biased sample and are not applicable to the noninstitutionalized Swedish epileptics as a whole.

Alström states on the first page of his monograph, "The clientele of epileptics at the Neurological clinic is probably more representative for this group of patients than the clienteles of mental hospitals and institutions for epileptics. These latter comprise a definite selection of psychically changed patients. But it is above all for the first-mentioned group of out-patients that the question of the hereditary nature of epilepsy plays an important practical note. Since the year 1757 we have had here in Sweden a law prohibiting marriage to patients suffering from so-called epilepsia idiopathia."

It is difficult to escape the impression that the author's primary purpose in undertaking this investigation was to expose the unfortunate aspects of this Swedish law. He devotes almost a quarter of the monograph directly or indirectly to a discussion of this law. While we can agree with the author that the only probable consequence of the law is to work unnecessary hardship on the mentally and socially competent epileptics and that it most probably accomplishes nothing of eugenic value, we feel that a separate pamphlet or monograph dealing with this topic would have served his purposes much more effectively not only with regard to combating the law but also with regard to the effectiveness of his medical, biological, and social analysis of the disease.

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Our Atomic Heritage

By ARNOLD B. GROBMAN (Department of Zoology, University of Florida). Gainesville: University of Florida Press, 1951. Pp. vii + 147. $2.95.

DURING World War II Dr. Grobman participated in a large-scale experiment designed to test the genetic effects of irradiation on mice. This experiment, which was under the direction of Dr. D. R. Charles, was one of a series of projects dealing with the biological effects of irradiation sponsored by the Manhattan Engineering District (later the U. S. Atomic

Energy Commission). A description of this experience, together with attempts to extrapolate from mice to man, comprise the first and major portion of the book, the remainder being devoted to a brief consideration of some of the applications of our expanding knowledge of nuclear fission, and some of the as yet essentially unsolved problems raised by the controlled release of atomic energy.

The present review will confine itself to a consideration of the first portion of the book. This is well written and reads easily. Unfortunately, however, it cannot be rated an accurate and lucid example of scientific reporting and inference. The author, after a description of the background and methods of the project, states that the experiment revealed that an irradiation dosage of about 40 roentgen (*r*) units doubles the mutation rate in mice. He then draws the reader's attention to the fact that the "tolerance limit" of employee irradiation established by the U. S. Atomic Energy Commission is 0.1 *r*/day, or 0.3 *r*/week. This is followed by the statements: "If these [mouse] figures are applicable to human beings, it means that 400 days of work, during which the radiation exposure is held to the currently accepted safe tolerance level of 0.1 *r*, would double a man's chance of having abnormal children .... Within a short period of normal working life and normal childbearing age, the danger of producing an abnormal child can change from negligible to appreciable, if a person is exposed to radiations that are currently considered safe."

There is an impressive amount of scientific misinformation packed into these two short sentences. The following specific points should be made:

1. Dr. Charles published a brief account of the results of his investigation in 1950 (*Radiology*, 55: 579). The control experiment revealed that each generation, in consequence of spontaneous mutation, approximately 15 out of each 10,000 gametes (.15 per cent) contain certain selected categories of newly arisen mutations. A radiation dose of 40 *r* will double that figure, increasing it to approximately 30 out of each 10,000 (.30 per cent). (The errors involved are relatively very large.) However, Dr. Charles' experiment was designed to pick up not only dominant gene mutations but also semi-sterilities due to chromosomal aberrations, as well as certain recessive mutations. Dr. Grobman implies that all of the various types of mutations detected in the mouse would in man result in abnormal first generation offspring, which is emphatically not the case.

2. Even if the effects of all those categories of mutation were apparent in the F_1, the rate of occurrence of abnormal children would not be doubled. The author apparently overlooked the fact that 1–2 per cent of all human pregnancies terminate in what he would loosely term an "abnormal" fashion. An exposure of 40 *r*, were we to accept his own figure, would result in an increase of from 1.00 per cent to 1.15 per cent, or perhaps from 2.00 per cent to 2.15 per cent.

3. It would have been well to point out that although 0.1 *r* is the accepted tolerance limit, every effort is made to minimize the irradiation exposure, and these efforts have to date been highly successful. It is a matter of record (*Eighth Semi-annual Report of the Atomic Energy Commission*) that the average *annual* exposure of employees at Hanford and Oak Ridge in 1949 was 0.2 *r*, while the average of the ten highest exposures in Oak Ridge workers was 4.2 *r* a year. The situation postulated by the author—so worded that the average reader will identify it with fact or near fact—simply does not exist.

4. The pitfalls involved in an extrapolation of this nature are varied and devious. The author gives a passing nod to them with the statement: "If these [mouse] figures are applicable to human beings . . ." But once the author has entered on this topic, the reader has a right to expect some treatment of the statistical errors involved, the possible differences in the sensitivity to irradiation of mouse and human chromosomes, the time factor in exposure, and the significance to his extrapolation of the probably higher spontaneous rate of muta-

tion of human genes. There are topics which are best not discussed at all if they cannot be discussed in proper perspective.

One would be inclined to dismiss this more lightly were it not for the fact that these statements can exercise a profound effect in a vital area of labor relations. It is well to recognize the genetic risks of irradiation, and the reviewer would be among the last to minimize these. But the problem should be viewed accurately and in its true proportions, as one among many perplexing dysgenic influences at work today. Observations are now under way in Hiroshima and Nagasaki, and experiments are in progress at Oak Ridge, which in the not-too-distant future should place this whole question on a firmer footing. In the meantime, there is little to be gained by presenting the public with so fragmentary and misleading an "inside story of the effects of radiation on heredity" (publisher's description).

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BIBLIOGRAPHY OF HUMAN GENETICS

THIS section, prepared by the Editor, continues the list of current research articles and books of special interest to students of human heredity, which was started with the first issue of Volume I, covering the year 1949. The present list constitutes part 3 for the year 1950; all publications listed bear the publication date of 1950. Abbreviations used for the titles of medical serials are those which have been adopted by the U. S. Army Medical Library, as published in the *Index-Catalogue of the Library of the Surgeon General's Office*, Fourth Series, volume 10, and in the *Current List of Medical Literature*. Articles published in this *Journal* are not included in the Bibliography.

In order to make the Bibliography of greater service, the address of each author, when known, is added in brackets following the citation. Except as otherwise noted, the address is that of the senior author in cases of multiple authorship. When two or more papers by the same author are listed, the address will be found at the end of the first reference cited.

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